SUPPLEMENTARY MATERIAL

for

Post-Synthetic Functionalization of Tryptophan-Containing Peptides through Indole (C-2) Photocatalytic Alkylation

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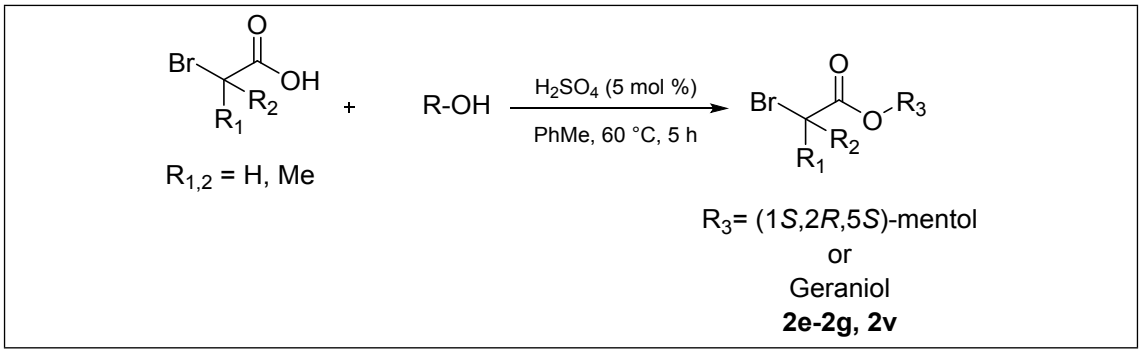
Contents

1. Details of general experimental procedures

Commercial supplies were used without further purification. Amino acids were all of L-configuration. Peptide synthesis was performed in liquid phase following the literature Procedure **A**.[1,2] ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AV400 (400 MHz ^{1}H frequency, 100 MHz ^{13}C frequency) instrument and are internally referenced to deuterated solvents $CDCl_3$ (δ_H 7.26, δ_C 77.2), acetone-d_6 (δ_H 2.84, δ_C 29.8) or DMSO-d_6 (δ_H 2.50, δ_C 39.5) ^{1}H and ^{13}C respectively, unless otherwise noted. Data for ^{1}H NMR are reported as follows: chemical shift (δ), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p= quintet, m = multiplet, dd =doublet of doublets, ddd= doublet of double doublets, dt = doublet of triplets), coupling constants (J) were reported in Hertz (Hz). High resolution mass spectra were recorded on a UPLC-ESI-QToF-MS using a Waters Acquity UPLC H-class liquid chromatograph coupled with a Waters Xevo G2-XS QToF mass spectrometer and electrospray interface (ESI). An ACQUITY BEH C_{18} column (2.1 x 100 mm, 1.7 µm; Waters Corporation) and mobile phase composed of H_2O + 0.1% formic acid (A) and MeCN + 0.1% formic acid (B) were used. The elution gradient started with 37% of B to 98% of B in 3.5 min and returned to 37% of B up 4.0 min, total time analysis of 5.0 min. The samples were prepared at a concentration of 10 µg mL^{-1}, and injected at 0.5 µL in a flow rate of 0.5 mL min^{-1}. Mass spectra were acquired in positive and resolution MSE Centroid mode, filtering mass from *m/z* 150 to 1000 in a scan time of 0.2 s and collision energy of 20-30 eV. ESI parameters were: capillary voltage of 2.2 kV, cone voltage of 40 V, source temperature of 100 ºC, desolvation temperature of 250 ºC, cone flow-gas of 50 L h^{-1} and desolvation gas flow of 550 L h^{-1}. Reactions were monitored by thin layer chromatography (TLC), using Merck silica gel 60 F254 glass plates (0.25 mm thick).

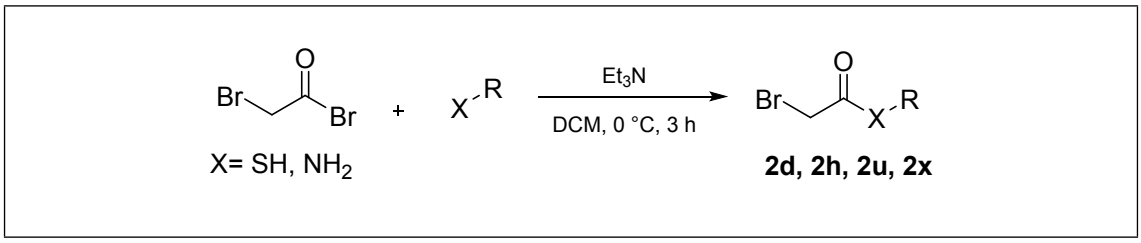
2. General synthesis of *α*-bromo-ester, amide, thiol and acyl derivatives (B)

According to the IUPAC nomenclature, compounds are named using ChemBioDraw 13.0 software (PerkinElmer).

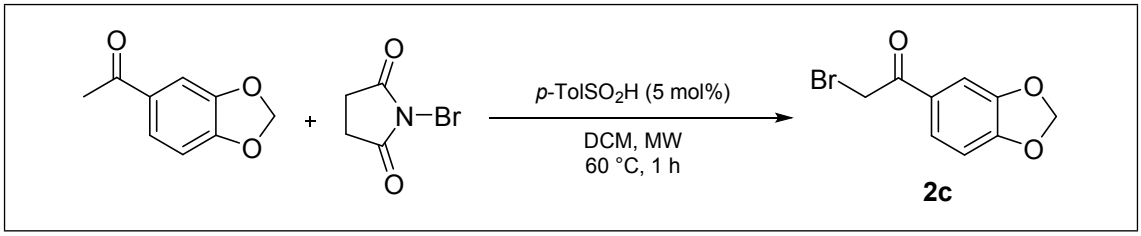


Procedure 1B. To a solution of alcohol [(1*S*,2*R*,5*S*)-2-isopropyl-5-methylcyclohexan-1-ol, or geraniol (5 mmol)] and an *α*-bromo acid (5 mmol) in toluene (5 mL) was added sulfuric acid (13.4 µL, 5 mol%). The reaction was heated to 60 °C. The resulting solution was stirred for 5 h. Then,

the reaction mixture was concentrated and the residue purified by flash column chromatography (Hexane/EtOAc, 9.5:0.5). Spectral data matched with those reported in literature.[3]

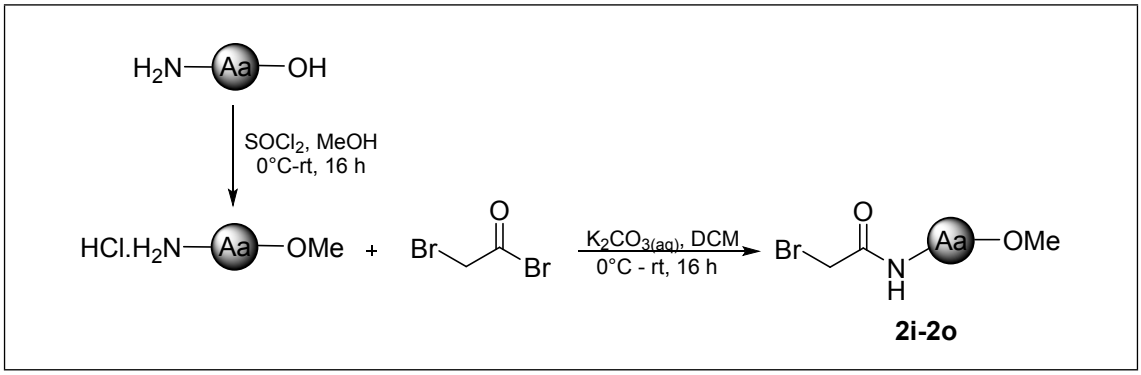


Procedure 2B. To 2-aminoisoindoline-1,3-dione, benzenethiol, eugenol or memantine chroride (5 mmol) in CH_2Cl_2 (15 mL) was added Et_3N (5 mmol) and 2-bromoacetyl bromide (644 µL, 7.5 mmol) dropwise at 0 °C. The resulting solution was stirred for 3 h. Then, the reaction mixture was concentrated and the residue purified by flash column chromatography (Hexane/EtOAc, 8:2). Spectral data matched with those reported in literature.[4]

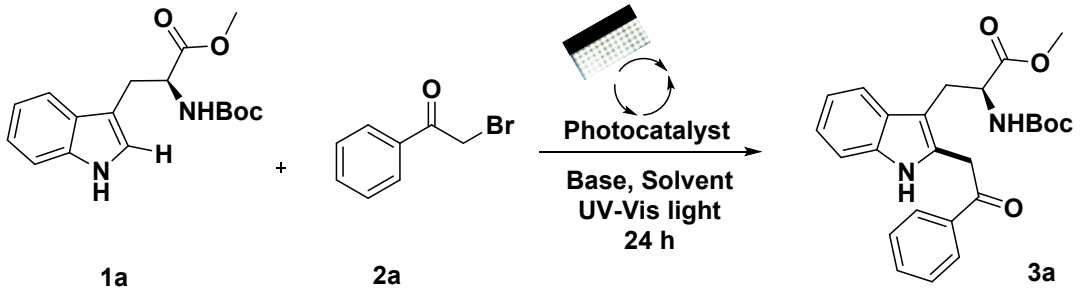


Procedure 3B. To a solution of 1-(benzo[d][1,3]dioxol-5-yl)ethan-1-one (82 mg, 0.5 mmol) in CH_2Cl_2 (5 mL) was added 1-bromopyrrolidine-2,5-dione (126 mg, 1.5 eq.), *p*-TsOH (5 mol%). The reaction was heated under microwave irradiation (150W) at 60 °C for 1 h. Then, the reaction mixture was concentrated and the residue purified by flash column chromatography (Hexane/EtOAc, 8:2). Spectral data matched with those reported in literature [5].

3. General synthesis of α-bromo-acetamides from amino acids and peptides (C)

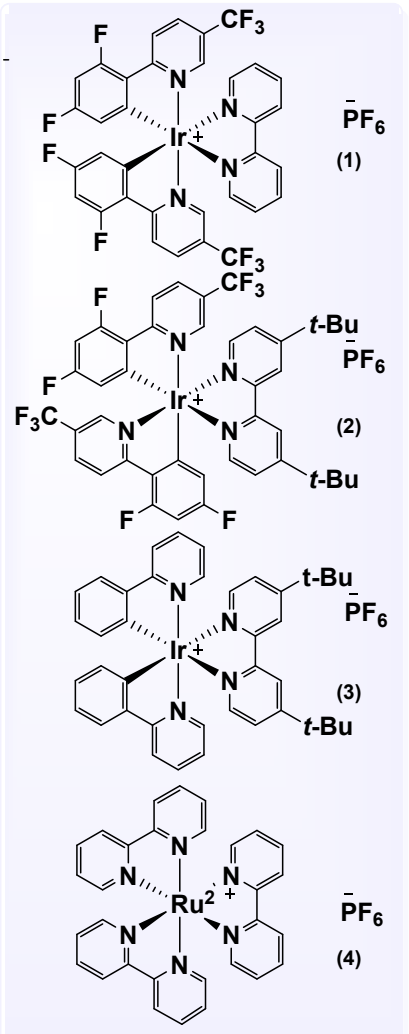


The products derived from L-Ala, L-Val, L-Ile, L-Glu, L-Met, L-Phe, and L-Pro were prepared according to literature procedure.[6] Spectral data matched with those reported in literature.[6]



1a **2a** **3a**

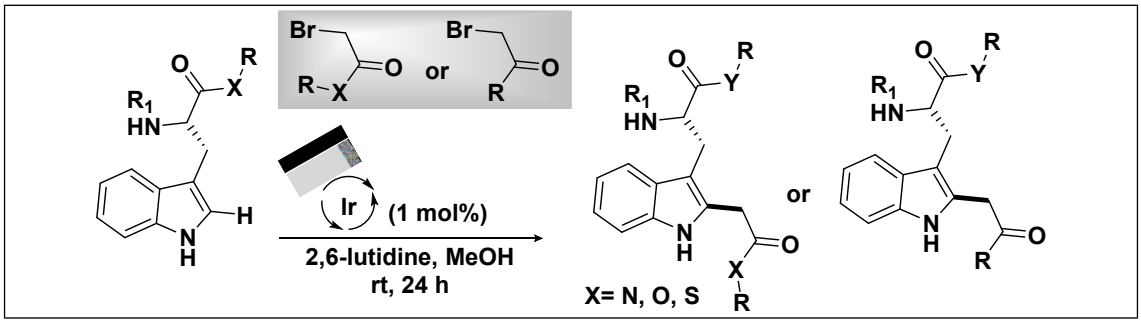
Entry	Deviation from Standard Conditions	3a (%)
1	**(1)**	57
2	No amine	n.r.
3	No photocatalyst	34
4	**(2)** instead of **(1)**	56
5	**(3)** instead of **(1)**	49
6	**(4)** instead of **(1)**	45
7	**(1)** and blue LED	Traces
8	**(4)** and blue LED	Traces
9	Entry 4 and no dried solvent	55
10[a]	Et_3N	Traces
11[a]	NMM	17
12[a]	4-$OCH_3N(Ph)_3$	Traces
13[a]	morpholine	Traces
14[a]	pyridine	44
15[a]	$NaHCO_3$	35
16[a]	*N,N*-$(CH_3)_2$pyridin-4-amine	n.r
17[a]	K_2CO_3	28
18[a]	3 equiv. of 2,6-lut.	**67**
19[a]	1 eq. of **1a** and 3 eq. of 2,6-lut.	53
20[a]	Entry 19 and 5 eq. of 2,6-lut.	51
21[a]	Entry 19 and 2 eq. of **2a**	53
22[a]	Entry 19 and 3 eq. of **2a**	25
23[a]	MeCN instead MeOH	26
24[a]	DMSO instead MeOH	23
25[a]	DMF instead MeOH	Traces
26[a]	EtOH instead MeOH	37
27[a]	Entry 18, Visible-light	61
28	no light	0



1a (0.2 mmol, 64 mg); **2b** (0.1 mmol, 20 mg); 2,6-lutidine (0.2 mmol); Catalyst (1 mol%); freezing-pump; dry solvent; Isolated yield. [a]Without dried solvent.

4. Optimization studies for photo-catalyzed alkylation of Trp 1a

5. General procedure to tryptophan-peptide photocatalytic alkylation (D)



Peptide (0.2 mmol, 2 equiv.), *α*-bromo-derivative (0.1 mmol, 1 equiv.), 2,6-lutidine (35 µL, 0.3 mmol, 3 equiv.), Ir{dFCF$_3$ppy}$_2$(bpy)}PF$_6$ (1-2 mol%) and MeOH (0.2 mL) were added into an oven-dried 10 mL Schlenk tube. The mixture was degassed by freeze-pump-thaw (3 times) of 2 min. The reaction mixture was then irradiated with two visible-light lamps (Kessil A360N E-Series Tuna Blue, 90W) for 24 hours. The reaction temperature was kept around 35 ºC with a cooling fan. The crude mixture was purified by flash column chromatography to afford the desired products (**3a-3m**, **4b-4z**).

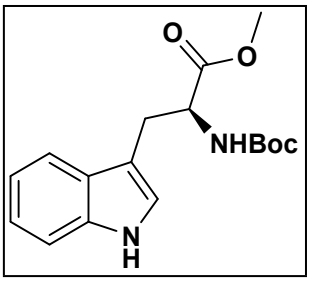
6. Procedure to 2,6-lutidine-mentol-salt synthesis (E)

The α-bromo-derivative (0.5 mmol, 1 equiv.), 2,6-lutidine (35 µL, 1.5 mmol, 3 equiv.) and MeOH (1.0 mL) were added into an oven-dried 10 mL Schlenk tube. The mixture was degassed by three round of freeze-pump-thaw of 2 min and left react in presence of visible-light lamps (Kessil A360N E-Series Tuna Blue, 90W) for 24 hours. The organic solvent was evaporated and to the crude reaction was added EtOAc, the precipitate was filtered and washed with EtOAc to obtain the pure solid.

7. Characterization data details

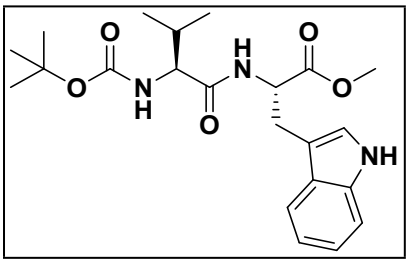
7.1. Characterization of Trp-peptides derivatives (1a-1n)

Methyl (tert-butoxycarbonyl)-L-tryptophanate



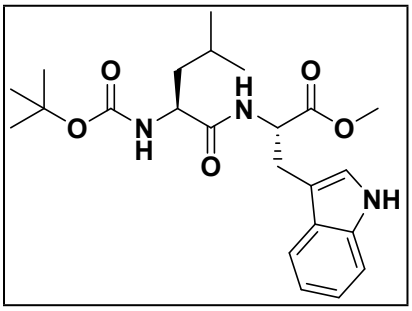
Compound **1a** was prepared following the general liquid phase synthesis procedure **A**. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.24 (s, 1H), 7.55 (d, *J* = 7.9 Hz, 1H), 7.34 (d, *J* = 8.1 Hz, 1H), 7.19 (t, *J* = 7.5 Hz, 1H), 7.12 (t, *J* = 7.4 Hz, 1H), 6.98 (s, 1H), 5.10 (d, *J* = 7.7 Hz, 1H), 4.65 (dd, *J* = 12.9, 5.6 Hz, 1H), 3.68 (s, 3H), 3.29 (s, 2H), 1.43 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 172.9, 155.4, 136.3, 127.8, 122.9, 122.3, 119.7, 118.8, 111.4, 110.2, 80.0, 54.4, 52.3, 28.4, 28.1. Spectral data matched with those reported in literature.[7]

Methyl (tert-butoxycarbonyl)-L-valyl-L-tryptophanate



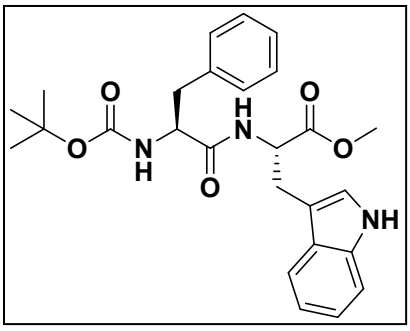
Compound **1b** was prepared following the general liquid phase synthesis procedure **A**. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.28 (s, 1H), 7.52 (d, *J* = 7.8 Hz, 1H), 7.33 (d, *J* = 8.0 Hz, 1H), 7.17 (t, *J* = 7.5 Hz, 1H), 7.11 (t, *J* = 7.4 Hz, 1H), 7.01 (s, 1H), 6.42 (d, *J* = 7.4 Hz, 1H), 5.07 (d, *J* = 8.3 Hz, 1H), 4.91 (q, *J* = 5.6 Hz, 1H), 3.94 (t, *J*= 7.2 Hz, 1H), 3.65 (s, 3H), 3.38 – 3.19 (m, 2H), 2.06 (m, 1H), 1.43 (s, 9H), 0.90 (d, *J* = 6.8 Hz, 3H), 0.83 (d, *J* = 6.2 Hz, 3H). Spectral data matched with those reported in literature.[8]

Methyl (tert-butoxycarbonyl)-L-leucyl-L-tryptophanate



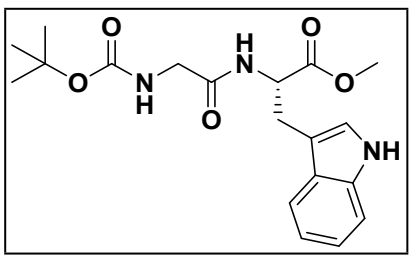
Compound **1c** was prepared following the general liquid phase synthesis procedure **A**. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.23 (s, 1H), 7.52 (d, *J* = 7.9 Hz, 1H), 7.33 (d, *J* = 8.1 Hz, 1H), 7.17 (t, *J* = 7.5 Hz, 1H), 7.10 (t, *J* = 7.4 Hz, 1H), 7.04 (s, 1H), 6.56 (d, *J* = 7.5 Hz, 1H), 4.89 (q, *J* = 5.4 Hz, 1H), 4.13 – 4.05 (m, 1H), 3.65 (s, 3H), 3.31 (d, *J* = 5.3 Hz, 2H), 1.64 – 1.54 (m, 2H), 1.41 (s, 9H), 1.29 (m, 1H), 0.90 – 0.84 (m, 6H). Spectral data matched with those reported in literature.[9]

Methyl (tert-butoxycarbonyl)-L-phenylalanyl-L-tryptophanate



Compound **1d** was prepared following the general liquid phase synthesis procedure **A**. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.11 (s, 1H), 7.29 (d, *J* = 7.6 Hz, 1H), 7.25 (d, *J* = 8.1 Hz, 1H), 7.21 – 7.13 (m, 4H), 7.10 (m, 2H), 6.99 (t, *J* = 7.4 Hz, 1H), 6.79 (s, 1H), 6.31 (d, *J* = 7.2 Hz), 4.86 (d, *J*= 7.2 Hz, 1H), 4.79 (q, *J* = 5.7 Hz, 1H), 4.26 (m, 1H), 3.55 (s, 3H), 3.17 (m, 2H), 2.94 (m, 2H), 1.23 (s, 9H). Spectral data matched with those reported in literature.[10]

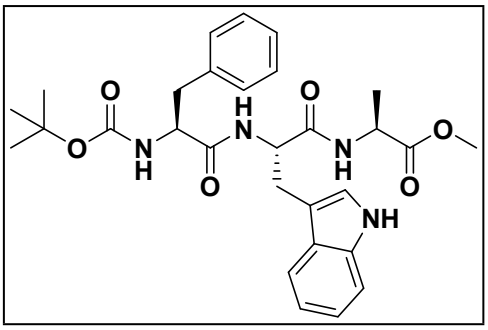
Methyl (tert-butoxycarbonyl)glycyl-L-tryptophanate



Compound **1e** was prepared following the general liquid phase synthesis procedure **A**. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.34 (s, 1H), 7.50 (d, *J* = 7.8 Hz, 1H), 7.33 (d, *J* = 8.1 Hz, 1H), 7.17 (t, *J* = 7.5 Hz, 1H), 7.10 (t, *J* = 7.4 Hz, 1H), 6.98 (s, 1H), 6.62 (d, *J* = 7.5 Hz, 1H), 5.11 (s, 1H), 4.91 (dt, *J* =

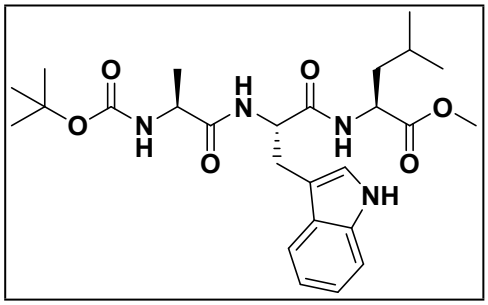
7.8, 5.4 Hz, 1H), 3.74 (m, 2H), 3.66 (s, 3H), 3.31 (d, *J* = 5.4 Hz, 2H), 1.42 (s, 9H). Spectral data matched with those reported in literature.[8]

Methyl (tert-butoxycarbonyl)-L-phenylalanyl-L-tryptophyl-L-alaninate



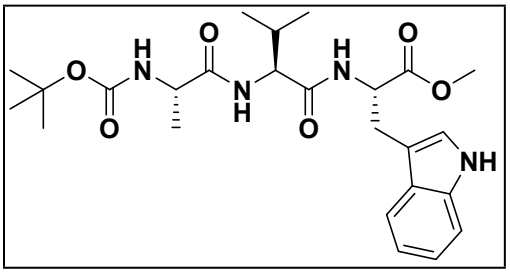
Compound **1f** was prepared following the general liquid phase synthesis procedure **A**. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.09 (s, 1H), 7.38 – 7.28 (m, 4H), 7.22 – 7.13 (m, 3H), 7.03 (m, 2H), 6.55 (d, *J* = 8.3 Hz, 1H), 6.40 (s, 1H), 4.70 (m, 2H), 4.31 (q, *J* = 6.4 Hz, 1H), 3.67 (s, 3H), 3.39 – 2.93 (m, 4H), 1.27 – 1.18 (m, 12H). Spectral data matched with those reported in literature.[11]

Methyl (tert-butoxycarbonyl)-L-alanyl-L-tryptophyl-L-leucinate



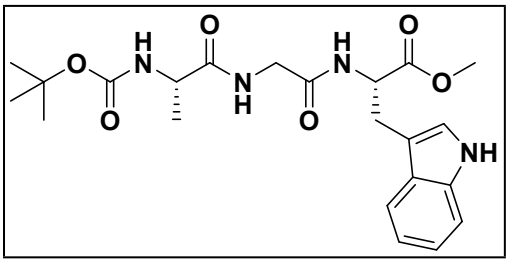
Compound **1g** was prepared following the general liquid phase synthesis procedure **A**. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.33 (s, 1H), 7.72 (d, *J* = 7.7 Hz, 1H), 7.38 (d, *J* = 8.0 Hz, 1H), 7.22 (t, *J* = 7.5 Hz, 1H), 7.16 (d, *J* = 7.6 Hz, 1H), 7.13 (s, 1H), 6.86 (d, *J* = 7.6 Hz, 1H), 6.39 (s, 1H), 4.92 (d, *J* = 6.5 Hz, 1H), 4.77 (q, *J* = 7.5 Hz, 1H), 4.50 (q, *J* = 8.1 Hz, 1H), 4.17 – 4.04 (m, 1H), 3.68 (s, 3H), 3.40 – 3.13 (m, 2H), 1.60 – 1.42 (m, 3H), 1.37 (s, 9H), 1.34 (d, *J* = 7.1 Hz, 3H), 0.85 (t, *J* = 5.8 Hz, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 172.9, 172.5, 171.0, 155.6, 136.4, 127.6, 123.7, 122.4, 119.9, 119.0, 111.4, 110.5, 80.3, 53.8, 52.3, 51.1, 50.8, 41.3, 28.3, 27.9, 24.7, 22.8, 22.0, 18.4. Spectral data matched with those reported in literature.[11]

Methyl (tert-butoxycarbonyl)-L-alanyl-L-valyl-L-tryptophanate



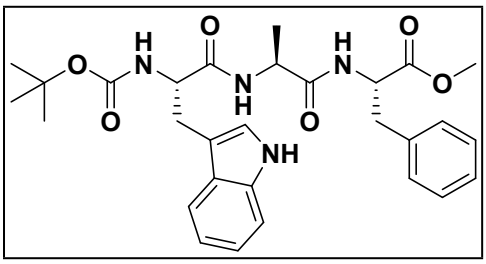
Compound **1h** was prepared following the general liquid phase synthesis procedure **A**. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.75 (s, 1H), 7.39 (d, *J* = 7.6 Hz, 1H), 7.17 (d, *J* = 7.8 Hz, 1H), 7.10 (d, *J* = 7.5 Hz, 1H), 6.99 (m, 2H), 6.84 (d, *J* = 1.6 Hz, 1H), 5.43 (s, 1H), 4.82 (dt, *J* = 13.2, 5.8 Hz, 1H), 4.39 (q, *J* = 8.4 Hz, 1H), 4.24 – 4.05 (m, 1H), 3.52 (s, 3H), 3.15 (d, *J* = 4.7 Hz, 2H), 1.98 (m, 1H), 1.33 (s, 9H), 1.11 (d, *J* = 7.0 Hz, 3H), 0.85 – 0.74 (m, 6H).**^{13}C NMR** (101 MHz, $CDCl_3$) δ 173.0, 172.2, 171.0, 155.7, 136.2, 127.5, 123.5, 122.2, 119.6, 118.5, 111.5, 109.4, 80.5, 58.4, 52.8, 52.5, 50.4, 31.2, 28.4, 27.6, 19.2, 18.0, 18.0. Spectral data matched with those reported in literature.[11]

Methyl (tert-butoxycarbonyl)-L-alanylglycyl-L-tryptophanate



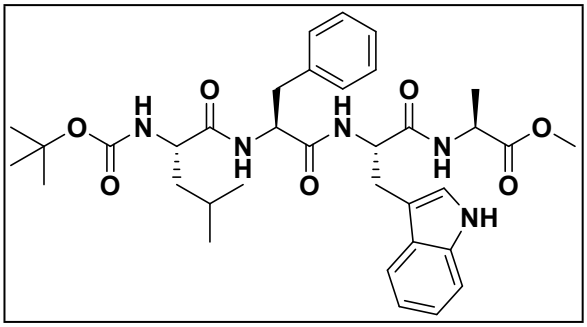
Compound **1i** was prepared following the general liquid phase synthesis procedure **A**. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.80 (s, 1H), 7.42 (d, *J* = 7.8 Hz, 1H), 7.21 (d, *J* = 8.0 Hz, 1H), 7.11 (d, *J* = 7.8 Hz, 1H), 7.04 (t, *J* = 7.5 Hz, 1H), 6.99 (t, *J* = 7.4 Hz, 1H), 6.85 (m, 2H), 5.21 (m, 1H), 4.79 (q, *J* = 7.0 Hz, 1H), 4.43 (p, *J*= 7.4 Hz, 1H), 3.61 (s, 3H), 3.58 – 3.34 (m, 2H), 3.26 – 3.10 (m, 2H), 1.37 (s, 9H), 1.15 (t, *J* = 12.0 Hz, 3H). Spectral data matched with those reported in literature.[12]

Methyl (tert-butoxycarbonyl)-L-tryptophyl-L-alanyl-L-phenylalaninate



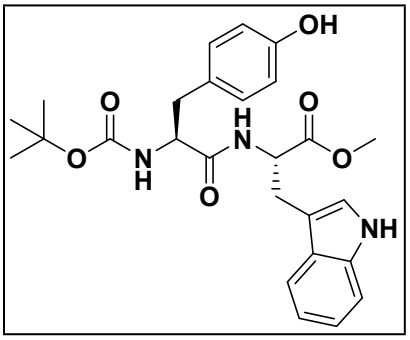
Compound **1j** was prepared following the general liquid phase synthesis procedure **A**. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.27 (s, 1H), 7.56 (d, *J* = 8.0 Hz, 1H), 7.25 (d, *J* = 8.1 Hz, 1H), 7.23 – 7.12 (m, 3H), 7.10 (t, *J* = 7.5 Hz, 1H), 7.04 (d, *J* = 7.6 Hz, 1H), 7.00 (d, *J* = 7.6 Hz, 2H), 6.88 (s, 1H), 6.64 (d, *J* = 7.5 Hz, 1H), 6.33 (d, *J* = 6.9 Hz, 1H), 5.15 (d, *J* = 6.8 Hz, 1H), 4.66 (q, *J* = 6.7 Hz, 1H), 4.32 (m, 2H), 3.60 (s, 3H), 3.23 – 3.04 (m, 2H), 3.02 - 2.86 (m, 2H), 1.34 (s, 9H), 1.07 (d, *J* = 7.0 Hz, 3H).**^{13}C NMR** (100 MHz, $CDCl_3$) δ 171.9, 171.8, 171.6, 155.7, 136.34, 136.0, 129.4, 128.7, 127.3, 123.4, 122.4, 119.8, 119.0, 111.4, 110.4, 80.3, 55.2, 53.6, 52.5, 49.0, 37.9, 28.4, 18.1. Spectral data matched with those reported in literature.[12]

Methyl (tert-butoxycarbonyl)-L-leucyl-L-phenylalanyl-L-tryptophyl-L-alaninate



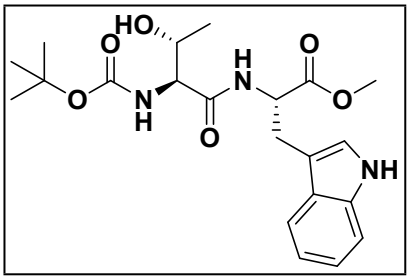
Compound **1k** was prepared following the general liquid phase synthesis procedure **A**. **^{1}H NMR** (300 MHz, DMSO-d_6) δ 10.80 (s, 1H), 8.37 (d, *J* = 6.8 Hz, 1H), 8.15 (d, *J* = 7.9 Hz, 1H), 7.68 (d, *J* = 8.2 Hz, 1H), 7.57 (d, *J* = 7.8 Hz, 1H), 7.30 (d, *J* = 8.0 Hz, 1H), 7.14 (m, 6H), 7.04 (t, *J* = 7.4 Hz, 1H), 6.96 (t, *J* = 7.4 Hz, 1H), 6.87 (d, *J* = 8.4 Hz, 1H), 4.63 – 4.44 (m, 2H), 4.28 (t, *J* = 7.1 Hz, 1H), 3.86 (m, 1H), 3.59 (s, 3H), 3.09 (dd, *J* = 15.0, 5.3 Hz, 1H), 3.01 – 2.86 (m, 2H), 2.78 (dd, *J* = 13.9, 9.1 Hz, 1H), 1.50-1.39 (m, 1H), 1.32 (s, 9H), 1.23 (d, *J* = 7.3 Hz, 3H), 0.78 (dd, *J* = 10.1, 6.6 Hz, 6H).**^{13}C NMR** (101 MHz, DMSO-d_6) δ 172.9, 172.2, 171.2, 170.8, 155.3, 137.5, 136.1, 129.4, 128.0, 127.4, 126.2, 123.7, 120.9, 118.5, 118.3, 111.3, 109.7, 78.2, 53.3, 53.1, 52.0, 47.7, 40.8, 37.8, 28.2, 27.8, 24.2, 23.0, 21.6, 17.0. Spectral data matched with those reported in literature.[12]

Methyl (tert-butoxycarbonyl)-L-tyrosyl-L-tryptophanate



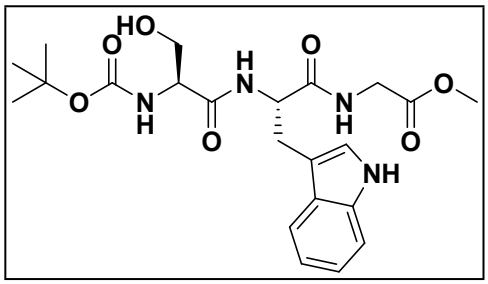
Compound **1l** was prepared following the general liquid phase synthesis procedure **A**. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.42 (s, 1H), 7.39 (d, *J* = 7.3 Hz, 1H), 7.32 (d, *J* = 8.2 Hz, 1H), 7.15 (t, *J* = 7.5 Hz, 1H), 7.07 (t, *J* = 7.2 Hz, 1H), 6.91 (m, 2H), 6.79 (s, 1H), 6.64 (d, *J* = 7.4 Hz, 2H), 6.24 (s, 1H), 5.12 (s, 1H), 4.80 (s, 1H), 4.25 (s, 1H), 3.54 (s, 3H), 3.21 (d, *J* = 4.4 Hz, 2H), 2.89 – 2.79 (m, 2H), 1.40 (s, 9H). Spectral data matched with those reported in literature.[13]

Methyl (tert-butoxycarbonyl)-L-threonyl-L-tryptophanate



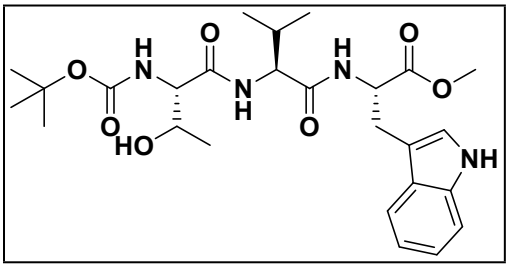
Compound **1m** was prepared following the general liquid phase synthesis procedure **A**. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.46 (s, 1H), 7.52 (d, *J* = 7.8 Hz, 1H), 7.32 (d, *J* = 8.0 Hz, 1H), 7.16 (t, *J* = 7.5 Hz, 1H), 7.10 (t, *J* = 7.4 Hz, 2H), 6.98 (d, *J* = 6.8 Hz, 1H), 5.48 (d, *J* = 7.8 Hz, 1H), 4.88 (q, *J* = 5.9 Hz, 1H), 4.29 – 4.22 (m, 1H), 4.10 (d, *J* = 7.0 Hz, 1H), 3.68 (s, 3H), 3.30 (d, *J* = 5.7 Hz, 2H), 1.40 (s, 9H), 1.13 (d, *J* = 6.4 Hz, 3H). Spectral data matched with those reported in literature.[14]

Methyl (tert-butoxycarbonyl)-L-seryl-L-tryptophylglycinate



Compound **1n** was prepared following the general liquid phase synthesis procedure **A**. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.78 (d, *J* = 1.5 Hz, 1H), 7.48 (d, *J* = 7.7 Hz, 1H), 7.22 (d, *J* = 7.9 Hz, 1H), 7.05 (t, *J* = 7.1 Hz, 1H), 6.98 (m, 3H), 5.66 (d, *J* = 7.0 Hz, 1H), 4.76 (q, *J* = 6.2 Hz, 1H), 4.09 (m, 1H), 3.91 – 3.64 (m, 3H), 3.50 (s, 3H), 3.32 – 3.10 (m, 2H), 1.28 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 172.1, 171.3, 170.4, 156.1, 136.3, 127.5, 123.8, 122.2, 119.7, 118.6, 111.5, 109.7, 80.6, 62.9, 56.0, 53.8, 52.5, 41.3, 28.3, 27.5. Spectral data matched with those reported in literature.[13]

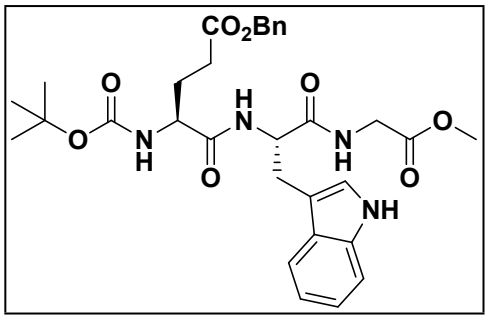
Methyl (tert-butoxycarbonyl)-L-threonyl-L-valyl-L-tryptophanate



Compound **1o** was prepared following the general liquid phase synthesis procedure **A**. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.76 (s, 1H), 7.49 (d, *J* = 7.9 Hz, 1H), 7.32 (d, *J* = 8.1 Hz, 1H), 7.14 (m, 2H), 7.08 (t, *J* = 7.4 Hz, 1H), 7.00 (d, *J* = 8.1 Hz, 1H), 6.98 (s, 1H), 5.64 (d, *J* = 7.8 Hz, 1H), 4.91 (q, *J* = 5.8 Hz, 1H),

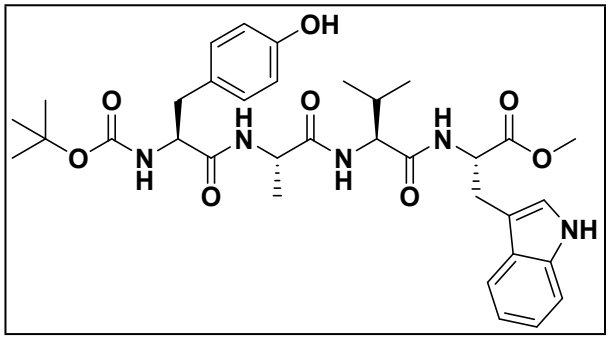
4.28 (t, *J* = 7.7 Hz, 1H), 4.07 (m, 2H), 3.66 (s, 3H), 3.26 (d, *J* = 5.5 Hz, 2H), 2.10 (m, 1H), 1.44 (s, 9H), 1.07 (d, *J* = 6.1 Hz, 3H), 0.88 (d, *J* = 6.7 Hz, 3H), 0.83 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.3, 171.6, 171.1, 156.6, 136.2, 127.4, 123.5, 122.1, 119.6, 118.4, 111.5, 109.4, 80.7, 67.0, 58.8, 58.3, 52.7, 52.6, 50.8, 30.7, 28.4, 27.7, 19.2, 18.4, 17.8. Spectral data matched with those reported in literature.[13]

Methyl (6S,9S)-9-((1H-indol-3-yl)methyl)-6-(3-(benzyloxy)-3-oxopropyl)-2,2-dimethyl-4,7,10-trioxo-3-oxa-5,8,11-triazatridecan-13-oate



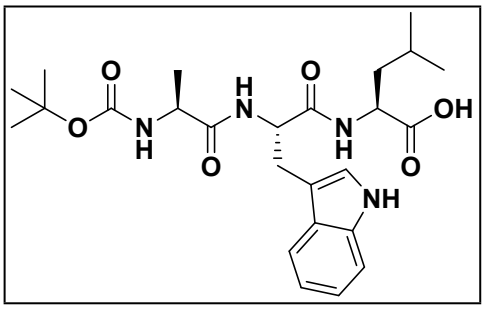
Compound **1p** was prepared following the general liquid phase synthesis procedure **A**. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.31 (s, 1H), 7.61 (d, *J* = 8.0 Hz, 1H), 7.43 – 7.28 (m, 6H), 7.16 (t, *J* = 7.5 Hz, 1H), 7.09 (s, 1H), 6.88 (d, *J* = 7.8 Hz, 1H), 6.79 (s, 1H), 5.35 (d, *J*= 5.0 Hz, 1H), 5.10 (s, 2H), 4.78 (q, *J* = 6.6 Hz, 1H), 4.05 (q, *J* = 5.9 Hz, 1H), 3.95 – 3.79 (m, 2H), 3.65 (s, 3H), 3.39 – 3.18 (m, 2H), 2.37 (t, *J* = 7.0 Hz, 2H), 1.96 – 1.77 (m, 2H), 1.33 (s, 9H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 173.4, 171.6, 171.5, 169.9, 156.1, 136.3, 135.8, 128.8, 128.5, 128.4, 127.6, 123.7, 122.3, 119.9, 118.7, 111.5, 110.1, 80.6, 66.8, 54.8, 53.8, 52.3, 41.3, 30.5, 28.3, 27.6, 27.2. Spectral data matched with those reported in literature.[13]

Methyl (tert-butoxycarbonyl)-L-tyrosyl-L-alanyl-L-valyl-L-tryptophanate



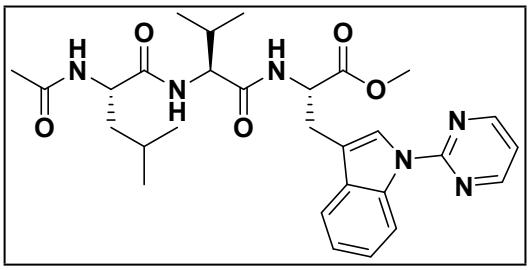
Compound **1q** was prepared following the general liquid phase synthesis procedure **A**. **^{1}H NMR** (300 MHz, DMSO-d_6) δ 10.84 (s, 1H), 9.13 (s, 1H), 8.37 (d, *J* = 7.0 Hz, 1H), 7.97 (d, *J* = 7.2 Hz, 1H), 7.74 (d, *J* = 9.0 Hz, 1H), 7.46 (d, *J* = 7.8 Hz, 1H), 7.32 (d, *J* = 8.0 Hz, 1H), 7.13 (d, *J* = 1.9 Hz, 1H), 7.09 – 6.91 (m, 4H), 6.82 (d, *J* = 8.5 Hz, 1H), 6.62 (d, *J* = 8.5 Hz, 2H), 4.50 (q, *J* = 7.1 Hz, 1H), 4.42 – 4.29 (m, 1H), 4.27 – 4.18 (dd, *J*= 8.8, 6.5 Hz, 1H), 4.09 – 3.98 (m, 1H), 3.52 (s, 3H), 3.19 – 3.00 (m, 2H), 2.89 – 3.53 (m, 2H), 1.95 (m, 1H), 1.28 (s, 9H), 1.17 (d, *J* = 6.8 Hz, 3H), 0.86-0.71 (m, 6H).**^{13}C NMR** (101 MHz, DMSO-d_6) δ 172.2, 172.0, 171.7, 171.1, 155.8, 155.4, 136.1, 130.2, 128.3, 127.1, 123.6, 121.1, 118.5, 118.0, 114.9, 111.5, 109.4, 78.1, 57.1, 56.1, 53.1, 51.8, 48.1, 36.6, 31.1, 28.2, 27.0, 19.1, 18.3, 17.9. Spectral data matched with those reported in literature.[15]

(Tert-butoxycarbonyl)-L-alanyl-L-tryptophyl-L-leucine



Compound **1s** was prepared following the general liquid phase synthesis procedure **A**. **^{1}H NMR** (400 MHz, DMSO-d6) δ = 10.82 (s, 1H), 8.22 (d, *J* = 8.0 Hz, 1H), 7.74 (d, *J* = 8.2 Hz, 1H), 7.57 (d, *J* = 7.9 Hz, 1H), 7.31 (d, *J* = 8.1 Hz, 1H), 7.24 (t, *J* = 7.4, 1H), 7.17 (d, *J* = 7.6 Hz, 1H), 7.15 – 7.11 (m, 1H), 7.05 (t, *J* = 7.5 Hz, 1H), 6.96 (t, *J* = 7.4 Hz, 2H), 4.61 – 6.53 (m, 1H), 4.29 – 4.22 (m, 1H), 3.94 – 3.96 (m, 1H), 3.18 – 2.92 (m, 2H), 1.66 – 1.55 (m, 1H), 1.54 – 1.49 (m, 2H), 1.35 (s, 9H), 1.10 (d, *J* = 7.2 Hz, 3H), 0.88 (d, *J* = 6.4 Hz, 3H), 0.82 (d, *J* = 6.3 Hz, 3H). **^{13}C NMR** (101 MHz, DMSO) δ = 174.0, 172.5, 171.3, 155.1, 136.1, 129.0, 123.7, 120.8, 118.5, 118.2, 111.3, 109.7, 78.2, 52.8, 50.3, 50.1, 28.2, 24.3, 22.9, 21.4, 18.1.Spectral data matched with those reported in literature.[15]

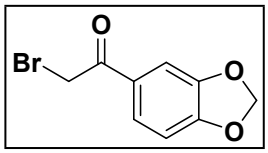
Methyl N$^{\alpha}$-acetyl-L-leucyl-L-valyl-1-(pyrimidin-2-yl)-L-tryptophanate



Compound **1s** was prepared following the general liquid phase synthesis procedure **A**. **^{1}H NMR** (300 MHz, DMSO-d_6) δ 8.82 (d, *J* = 4.8 Hz, 2H), 8.70 (d, *J* = 8.2 Hz, 1H), 8.44 (d, *J* = 7.1 Hz, 1H), 8.16 (s, 1H), 7.98 (d, *J* = 8.2 Hz, 1H), 7.60 (t, *J* = 8.1 Hz, 1H), 7.34 – 7.27 (m, 1H), 7.22 (t, *J* = 7.1 Hz, 1H), 4.58 (dd, *J* = 14.0, 7.2 Hz, 1H), 4.27 (q, *J* = 7.8 Hz, 1H), 4.18 (dd, *J* = 8.9, 6.8 Hz, 1H), 3.56 (s, 3H), 3.16 (dd, *J* = 14.8, 7.0 Hz, 2H), 1.93 (m, 1H), 1.81 (s, 3H), 1.50 (m, 1H), 1.33 (t, *J* = 7.2 Hz, 2H), 0.76 (m 12H). Spectral data matched with those reported in literature.[15]

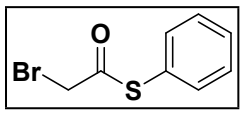
7.2. Characterization of starting materials α-bromo-derivatives (2c-2o, 2u-2z)

1-(benzo[d][1,3]dioxol-5-yl)-2-bromoethan-1-one



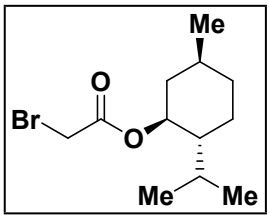
Compound **2c** was prepared according to general procedure **3B**. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.59 (d, *J* = 8.2 Hz, 1H), 7.45 (s, 1H), 6.88 (d, *J* = 8.2 Hz, 1H), 6.07 (s, 2H), 4.37 (s, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 189.7, 152.7, 148.6, 128.8, 125.7, 108.7, 108.3, 102.3, 30.7. Spectral data matched with those reported in literature.[16]

S-phenyl 2-bromoethanethioate



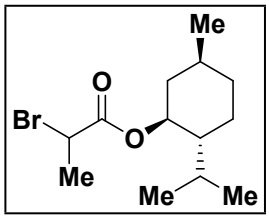
Compound **2d** was prepared according to general procedure **2B**. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.44 (m, 5H), 4.13 (s, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 191.2, 134.7, 130.1, 129.6, 126.9, 33.3. Spectral data matched with those reported in literature.[17]

(1S,2R,5S)-2-isopropyl-5-methylcyclohexyl 2-bromoacetate



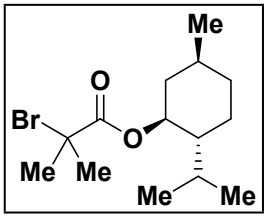
Compound **2e** was prepared according to general procedure **1B** .**^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.73 (td, *J* = 10.9, 4.4 Hz, 1H), 3.84 – 3.77 (m, 2H), 2.01 (d, *J* = 12.0 Hz, 1H), 1.95 – 1.83 (m, 1H), 1.69 (d, *J* = 11.1 Hz, 2H), 1.55 – 1.35 (m, 2H), 1.12 – 0.95 (m, 2H), 0.94 – 0.87 (m, 6H), 0.81-0.86 (m, 1H), 0.76 (d, *J* = 7.0 Hz, 3H).**^{13}C NMR** (100 MHz, $CDCl_3$) δ 167.0, 76.6, 47.1, 40.6, 34.3, 31.5, 26.4, 26.3, 23.5, 22.1, 20.9, 16.4. Spectral data matched with those reported in literature.[18]

(1S,2R,5S)-2-isopropyl-5-methylcyclohexyl (±)-2-bromopropanoate



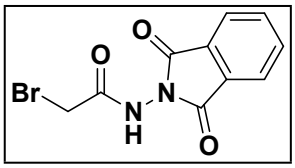
Compound **2f** was prepared according to general procedure **1B**. **^{1}H NMR** (400 MHz, $CDCl_3$) δ (diasteroisomers) 4.76 – 4.63 (m, 1H), 4.34 (q, *J* = 6.9 Hz, 1H), 2.03 – 1.84 (m, 2H), 1.81 (d, *J* = 6.9 Hz, 3H), 1.69 (d, *J* = 11.1 Hz, 2H), 1.44 (m, 2H), 1.14 – 0.94 (m, 2H), 0.91 (m, 7H), 0.76 (d, *J* = 7.0 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ (diasteroisomers)170.0, 170.0, 76.1, 47.2, 47.0, 41.0, 40.8, 40.6, 40.3, 34.3, 31.5, 31.5, 26.3, 26.1, 23.5, 23.4, 22.1, 21.8, 21.7, 20.9, 20.9, 16.4, 16.2. Spectral data matched with those reported in literature.[3]

(1S,2R,5S)-2-isopropyl-5-methylcyclohexyl 2-bromo-2-methylpropanoate



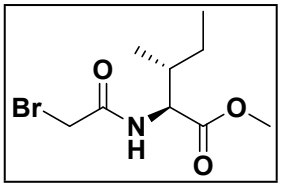
Compound **2g** was prepared according to general procedure **1B. ^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.69 (td, *J* = 10.9, 4.4 Hz, 1H), 2.03 – 1.94 (m, 2H), 1.92 (s, 6H), 1.70 (d, *J* = 11.0 Hz, 2H), 1.48 (t, *J* = 11.6 Hz, 2H), 1.13 – 0.95 (m, 2H), 0.93 – 0.88 (m, 6H), 0.86 (m, 1H), 0.77 (d, *J* = 7.0 Hz, 3H).**^{13}C NMR** (100 MHz, $CDCl_3$) δ 171.3, 76.2, 56.5, 47.2, 40.3, 34.4, 31.5, 30.9, 30.9, 26.3, 23.4, 22.2, 20.9, 16.3. Spectral data matched with those reported in literature.[3]

2-bromo-N-(1,3-dioxoisoindolin-2-yl)acetamide



Compound **2h** was prepared according to general procedure **2B**. **^{1}H NMR** (400 MHz, acetone-d_6) δ 7.38 (m, 4H), 3.59 (s, 2H). **^{13}C NMR** (100 MHz, acetone-d_6) δ 166.4, 165.5, 135.9, 130.9, 124.5, 26.2. Spectral data matched with those reported in literature.[4]

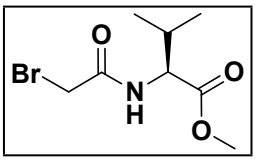
Methyl (2-bromoacetyl)-L-alloisoleucinate



Compound **2i** was prepared according to general procedure **C. ^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.93 (d, *J*= 8.7 Hz, 1H), 4.57 (dd, *J* = 8.5, 4.8 Hz, 1H), 3.90 (s, 2H), 3.76 (s, 3H), 2.00 – 1.87 (m, 1H), 1.51 – 1.39 (m, 1H), 1.27 – 1.13 (m, 1H), 0.94 (m, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 171.9,

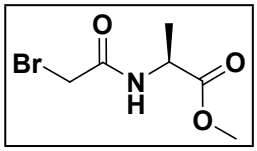
165.4, 57.2, 52.4, 38.0, 29.1, 25.3, 15.5, 11.7. Spectral data matched with those reported in literature.[6]

Methyl (2-bromoacetyl)-L-valinate



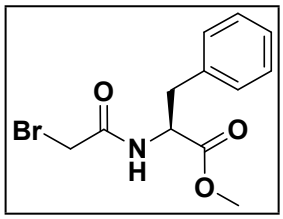
Compound **2j** was prepared according to general procedure **C**. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.91 (d, *J* = 7.4 Hz, 1H), 4.53 (dd, *J* = 8.7, 4.8 Hz, 1H), 3.91 (s, 2H), 3.76 (s, 3H), 2.22 (m, 1H), 0.95 (m, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 171.9, 165.5, 57.8, 52.5, 31.5, 29.1, 19.0, 17.8. Spectral data matched with those reported in literature.[6]

Methyl (2-bromoacetyl)-L-alaninate



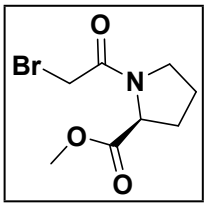
Compound **2k** was prepared according to general procedure **C**. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.01 (s, 1H), 4.57 (p, *J* = 7.2 Hz, 1H), 3.88 (s, 2H), 3.77 (s, 3H), 1.45 (d, *J* = 7.2 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 173.0, 165.2, 52.9, 48.9, 28.9, 18.3. Spectral data matched with those reported in literature.[6]

Methyl (2-bromoacetyl)-L-phenylalaninate



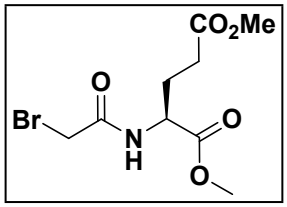
Compound **2l** was prepared according to general procedure **C**. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.29 – 7.09 (m, 3H), 7.05 (d, *J* = 7.2 Hz, 2H), 6.78 (d, *J* =7.9 Hz, 1H), 4.78 (q, 5.9 Hz, 1H), 3.83 – 3.70 (m, 2H), 3.66 (s, 3H), 3.16 – 2.92 (m, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 171.4, 165.2, 135.4, 129.4, 128.8, 127.5, 53.8, 52.6, 37.8, 28.8. Spectral data matched with those reported in literature.[6]

Methyl (2-bromoacetyl)-L-prolinate



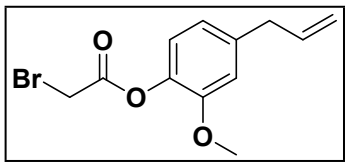
Compound **2m** was prepared according to general procedure **C**. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.52 (dd, *J* = 8.6, 3.7 Hz, 1H), 3.85 (m, 2H), 3.75 (s, 3H), 3.74 – 3.58 (m, 2H), 2.38 – 1.98 (m, 4H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 172.3, 165.4, 59.3, 52.5, 47.6, 29.3, 27.1, 25.0. Spectral data matched with those reported in literature.[6]

Dimethyl (2-bromoacetyl)-L-glutamate



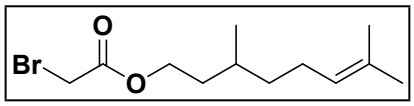
Compound **2o** was prepared according to general procedure **C**. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.12 (d, *J* = 7.8 Hz, 1H), 4.60 (m, 1H), 3.87 (s, 2H), 3.76 (s, 3H), 3.68 (s, 3H), 2.48 – 2.30 (m, 2H), 2.25 (m, 1H), 2.04 (m, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 173.2, 171,8, 165.8, 52.8, 52.4, 52.1, 30.0, 28.7, 27.1. Spectral data matched with those reported in literature.[6]

2-methoxy-4-vinylphenyl 2-bromoacetate



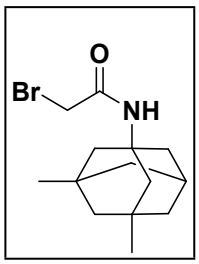
Compound **2u** was prepared according to general procedure **2B**. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.98 (d, *J* = 8.0 Hz, 1H), 6.80 (s, 1H), 6.78 (d, *J* = 8.5 Hz, 1H), 5.95 (m, 1H), 5.12 (d, *J* = 8.1 Hz, 1H), 5.09 – 5.07 (m, 1H), 4.08 (s, 2H), 3.82 (s, 3H), 3.38 (d, *J* = 6.7 Hz, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 165.6, 150.8, 139.7, 137.7, 137.0, 122.2, 120.8, 116.4, 112.9, 56.0, 40.2, 25.5. Spectral data matched with those reported in literature. [6]

3,7-dimethyloct-6-en-1-yl 2-bromoacetate



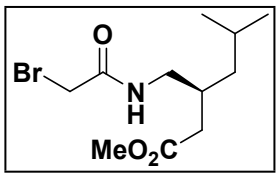
Compound **2v** was prepared according to general procedure **1B**. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.08 (t, *J* = 7.0 Hz, 1H), 4.26 – 4.15 (m, 2H), 3.82 (s, 2H), 2.06 – 1.90 (m, 2H), 1.80-1.71 (m, 1H), 1.68 (s, 3H), 1.59 (s, 3H), 1.52-1.42 (m, 2H), 1.40 – 1.27 (m, 1H), 1.27 – 1.11 (m, 2H), 0.92 (d, *J* = 6.5 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 167.5, 131.6, 124.6, 65.0, 37.0, 35.3, 29.4, 26.1, 25.9, 25.5, 19.5, 17.8. Spectral data matched with those reported in literature.[3]

2-bromo-N-(3,5-dimethyladamantan-1-yl)acetamide



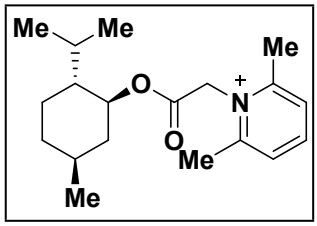
Compound **2x** was prepared according to general procedure **2B**. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.80 (s, 1H), 3.76 (s, 2H), 2.15 (q, *J* = 3.2 Hz, 1H), 1.84 (s, 2H), 1.64 (td, *J* = 22.0, 11.7 Hz, 4H), 1.33 (td, *J*= 36.9, 12.9 Hz, 4H), 1.16 (td, *J* = 23.8, 6.9 Hz, 2H), 0.85 (s, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 164.3, 54.3, 50.6, 47.2, 42.6, 39.8, 32.5, 30.1, 30.1. Spectral data matched with those reported in literature.[4]

Methyl (S)-3-((2-bromoacetamido)methyl)-5-methylhexanoate



Compound **2z** was prepared according to general procedure **3C**. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.17 (s, 1H), 3.87 (s, 2H), 3.69 (s, 3H), 3.36 (dt, *J* = 13.4, 5.3 Hz, 1H), 3.18 (dt, *J* = 13.7, 6.9 Hz, 1H), 2.40 – 2.23 (m, 2H), 2.20 (m, 1H), 1.64 (m, 1H), 1.17 (m, 2H), 0.89 (dd, *J* = 9.7, 6.5 Hz, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 173.6, 165.6, 51.8, 43.9, 41.7, 37.3, 33.0, 29.2, 25.2, 22.7, 22.6. Spectral data matched with those reported in literature.[6]

1-(2-(((1S,2R,5S)-2-isopropyl-5-methylcyclohexyl)oxy)-2-oxoethyl)-2,6-dimethylpyridin-1-ium

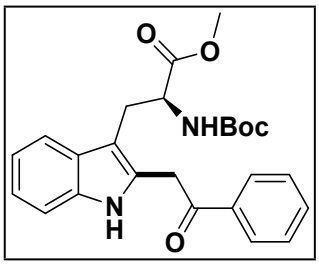


Compound **lutidine-salt** was prepared according to general procedure **E**. **^{1}H NMR** (400 MHz, MeOH-d_4) δ 8.42 (t, *J* = 7.9 Hz, 1H), 7.96 (d, *J* = 7.9 Hz, 2H), 5.63 (s, 2H), 4.89 (dt, *J* = 11.0, 5.5 Hz, 1H), 2.83 (s, 6H), 2.15 – 2.02 (m, 1H), 1.86 (dq, *J* = 11.4, 4.4, 3.5 Hz, 1H), 1.81 – 1.64 (m, 2H), 1.56 – 1.41 (m, 2H), 1.22 – 1.05 (m,

2H), 0.94 (t, J = 6.8 Hz, 6H), 0.79 (d, J = 7.0 Hz, 3H). **^{13}C NMR** (100 MHz, MeOH-d_4) δ 166.3, 158.1, 147.3, 129.1, 79.1, 55.1, 41.6, 35.1, 32.7, 27.5, 24.2, 22.3, 21.6, 21.1, 16.3. **HRMS (ESI):** m/z calc. for $C_{19}H_{30}NO_2$ $[M+H]^+$ 304.2271, found 304.2274.

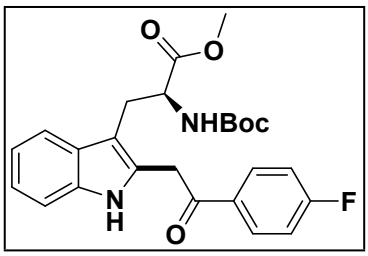
7.3. Characterization of tryptophan C-2 functionalization

Methyl (S)-2-((tert-butoxycarbonyl)amino)-3-(2-(2-oxo-2-phenylethyl)-1H-indol-3-yl)propanoate



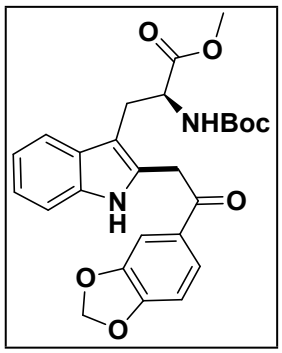
Compound **3a** was prepared according to general procedure **D**, methyl (tert-butoxycarbonyl)-*L*-tryptophanate (64 mg, 0.20 mmol) and 2-bromo-1-phenylethan-1-one (20 mg, 0.10 mmol). Flash column chromatography purification (CH_2Cl_2/EtOAc 9:1) afforded compound **3a** (29 mg, 67%) as an yellow amorphous solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.83 (s, 1H), 8.07 (d, J = 7.7 Hz, 2H), 7.61 (t, J = 7.4 Hz, 1H), 7.51 (t, J = 7.7 Hz, 2H), 7.32 (d, J = 8.0 Hz, 1H), 7.15 (t, J = 7.5 Hz, 1H), 7.08 (t, J = 7.5 Hz, 1H), 5.19 (d, J = 8.2 Hz, 1H), 4.64 (d, J = 6.9 Hz, 1H), 4.47 (d, J = 3.5 Hz, 2H), 3.58 (s, 3H), 3.33 (dq, J = 14.7, 5.5 Hz, 2H), 1.39 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 197.4, 172.8, 155.4, 136.4, 136.0, 134.0, 129.5, 129.1, 128.6, 128.3, 122.1, 119.7, 118.5, 111.0, 107.7, 80.0, 54.4, 52.5, 35.1, 28.4, 27.6. **HRMS (ESI):** m/z calc. for $C_{25}H_{28}N_2NaO_5$ $[M+H]^+$ 459.1890, found 459.1895.

Methyl (S)-2-((tert-butoxycarbonyl)amino)-3-(2-(2-(4-fluorophenyl)-2-oxoethyl)-1H-indol-3-yl)propanoate



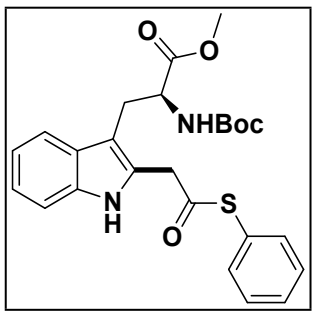
Compound **3b** was prepared according to general procedure **D**, Boc-Trp-OMe (64 mg, 0.20 mmol) and 2-bromo-1-(4-fluorophenyl)ethan-1-one (22 mg, 0.10 mmol). Flash column chromatography purification (CH_2Cl_2/ EtOAc 9.5:0.5) afforded compound **3b** (25 mg, 55%) as an yellow amorphous solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.82 (s, 1H), 8.15 – 8.03 (m, 2H), 7.47 (d, J = 7.3 Hz, 1H), 7.33 (d, J=8.1 Hz, 1H), 7.20 – 7.11 (m, 3H), 7.08 (t, J = 7.4 Hz, 1H), 5.20 (d, J = 7.4 Hz, 1H), 4.62 (q, J = 6.4 Hz, 1H), 4.53 – 4.37 (m, 2H), 3.57 (s, 3H), 3.41 – 3.21 (m, 2H), 1.40 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 172.8, 167.6, 165.1, 155.4, 136.0, 132.8, 131.5, 131.4, 129.3, 128.2, 122.1, 119.7, 118.5, 116.3, 116.1, 111.1, 107.8, 80.1, 54.5, 52.6, 35.3, 28.4, 27.7. **^{19}F NMR** (377 MHz, $CDCl_3$) δ -103.6. **HRMS (ESI):** m/z calc. for $C_{25}H_{27}FN_2NaO_5$ $[M+Na]^+$ 477.1796, found 477.1798.

Methyl (S)-3-(2-(2-(benzo[d][1,3]dioxol-5-yl)-2-oxoethyl)-1H-indol-3-yl)-2-((tert-butoxycarbonyl)amino)propanoate



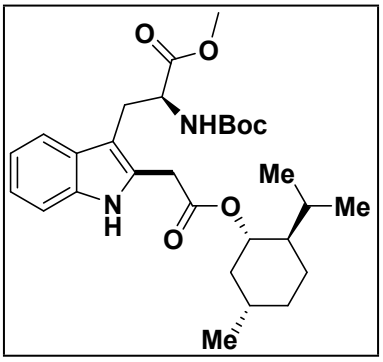
Compound **3c** was prepared according to general procedure **D**, Boc-Trp-OMe (64 mg, 0.20 mmol) and 1-(benzo[*d*][1,3]dioxol-5-yl)-2-bromoethan-1-one (24 mg, 0.10 mmol). Flash column chromatography purification (CH_2Cl_2/ EtOAc 9.5:0.5) afforded compound **3c** (22 mg, 45%) as a brown liquid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.84 (s, 1H), 7.70 (d, *J* = 8.1 Hz, 1H), 7.49 (s, 1H), 7.47 (d, *J* = 8.0 Hz, 1H), 7.31 (d, *J* = 7.9 Hz, 1H), 7.13 (t, *J* = 7.7 Hz, 1H), 7.09 (t, *J* = 7.5 Hz, 1H), 6.89 (d, *J* = 8.2 Hz, 1H), 6.07 (s, 2H), 5.21 (d, *J* = 7.7 Hz, 1H), 4.63 (q, *J* = 5.1 Hz, 1H), 4.38 (m, 2H), 3.59 (s, 3H), 3.32 (m, 2H), 1.41 (s, 9H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 195.4, 172.9, 155.4, 152.6, 148.6, 135.9, 131.2, 129.7, 125.3, 122.0, 119.6, 118.5, 111.0, 108.2, 107.5, 102.2, 80.0, 54.5, 52.5, 34.8, 28.4, 27.6. **HRMS (ESI):** m/z calc. for $C_{26}H_{28}N_2NaO_7$ $[M+Na]^+$ 503.1789, found 503.1799.

Methyl (S)-2-((tert-butoxycarbonyl)amino)-3-(2-(2-oxo-2-(phenylthio)ethyl)-1H-indol-3-yl)propanoate



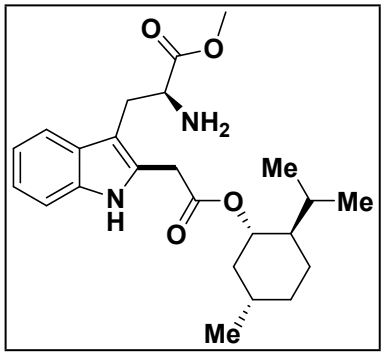
Compound **3d** was prepared according to general procedure **D**, Boc-Trp-OMe (64 mg, 0.20 mmol) and *S*-phenyl 2-bromoethanethioate (23 mg, 0.10 mmol). Flash column chromatography purification (CH_2Cl_2/ EtOAc 9.5:0.5) afforded compound **3d** (23 mg, 48%) as an brown liquid**. ^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.50 (s, 1H), 7.43 (d, *J* = 8.0 Hz, 1H), 7.30-7.36 (m, 5H), 7.20 (d, *J* = 9.6 Hz, 1H), 7.08 (t, *J* = 7.5 Hz, 1H), 7.02 (t, *J* = 7.4 Hz, 1H), 5.13 (d, *J* = 7.8 Hz, 1H), 4.58 (q, *J* = 6.8 Hz, 1H), 4.00 (s, 2H), 3.57 (s, 3H), 3.23 (d, *J* = 5.6 Hz, 2H), 1.35 (s, 9H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 195.1, 172.8, 155.29, 135.92, 134.56, 129.94, 129.45, 127.95, 127.09, 122.45, 119.88, 118.81, 111.02, 108.53, 80.07, 54.33, 52.54, 40.23, 28.46, 27.41. **HRMS (ESI):** m/z calc. for $C_{25}H_{28}N_2NaO_5S$ $[M+Na]^+$ 491.1611, found 491.1620.

Methyl (S)-2-((tert-butoxycarbonyl)amino)-3-(2-(2-(((1S,2R,5S)-2-isopropyl-5-methylcyclohexyl)oxy)-2-oxoethyl)-1H-indol-3-yl)propanoate



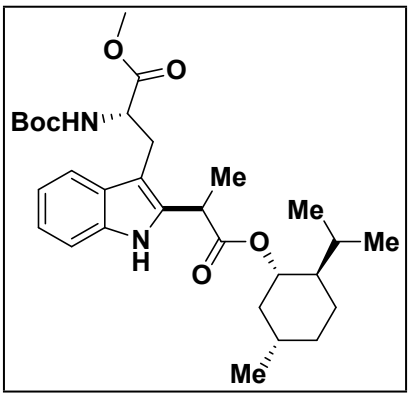
Compound **3e** was prepared according to general procedure **D**, Boc-Trp-OMe (64 mg, 0.20 mmol) and (1*S*,2*R*,5*S*)-2-isopropyl-5-methylcyclohexyl 2-bromoacetate (28 mg, 0.1 mmol). Flash column chromatography purification (CH_2Cl_2/ EtOAc 9.5:0.5) afforded compound **3e** (39 mg, 76%) as a light yellow amorphous solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.80 (s, 1H), 7.40 (d, *J* = 7.8 Hz, 1H), 7.23 (d, *J* = 8.0 Hz, 1H), 7.04 (m, 2H), 5.10 (d, *J* = 7.6 Hz, 1H), 4.68 (td, *J* = 10.8, 4.3 Hz, 1H), 4.53 (m, 1H), 3.70 (s, 2H), 3.55 (s, 3H), 3.17 (d, *J* = 5.5 Hz, 2H), 1.92 (d, *J* = 12.0 Hz, 1H), 1.79 – 1.67 (m, 1H), 1.67 – 1.54 (m, 2H), 1.45 – 1.35 (m, 1H), 1.35 (s, 9H), 1.18 (t, *J* = 7.3 Hz, 2H), 1.08 – 0.87 (m, 2H), 0.83 (d, *J* = 6.7 Hz, 3H), 0.79 (d, *J* = 6.9 Hz, 3H), 0.65 (d, *J* = 6.9 Hz, 3H).**^{13}C NMR** (100 MHz, $CDCl_3$) δ 172.8, 170.5, 155.2, 135.7, 128.9, 128.4, 122.0, 119.7, 118.5, 110.9, 107.5, 79.9, 75.7, 54.3, 52.4, 47.1, 40.9, 34.2, 31.8, 31.5, 28.4, 27.3, 26.3, 23.5, 22.1, 20.8, 16.4. **HRMS (ESI):** m/z calc. for $C_{29}H_{42}N_2NaO_6$ $[M+Na]^+$ 537.2935, found 537.2940.

Methyl (S)-2-amino-3-(2-(2-(((1S,2R,5S)-2-isopropyl-5-methylcyclohexyl)oxy)-2-oxoethyl)-1H-indol-3-yl)propanoate



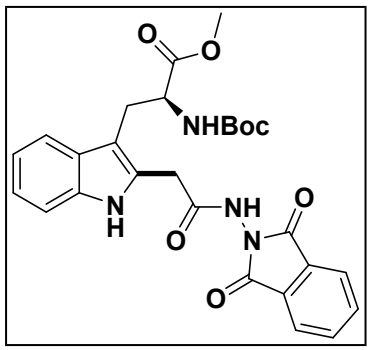
Compound **3e[a]** was prepared according to general procedure **D**, HCl.NH_2-Trp-OMe 51 mg, 0.20 mmol) and (1*S*,2*R*,5*S*)-2-isopropyl-5-methylcyclohexyl 2-bromoacetate (28 mg, 0.1 mmol). Flash column chromatography purification (Hexane/ EtOAc 7:3) afforded compound **3e[b]** (15 mg, 35%) as a brown solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.17 (s, 1H), 7.61 (d, *J* = 7.9 Hz, 1H), 7.35 (d, *J* = 8.1 Hz, 1H), 7.19 (t, *J* = 7.5 Hz, 1H), 7.16 – 7.08 (m, 1H), 3.70 (t, *J* = 6.5 Hz, 1H), 3.66 (s, 3H), 3.46– 3.30 (m, 2H), 3.30 – 3.13 (m, 2H), 2.13 (s, 2H, -NH_2), 1.92 (d, *J* = 11.9 Hz, 1H), 1.81 – 1.69 (m, 1H), 1.69 – 1.58 (m, 1H), 1.49 – 1.37 (m, 1H), 1.28 – 1.16 (m, 1H), 0.97 – 0.74 (m, 1H), 0.86 (m, 8H), 3.09 (d, *J* = 6.9 Hz, 3H). δ **^{13}C NMR** (100 MHz, $CDCl_3$) δ 174.4, 171.3, 136.4, 127.5, 123.2, 122.3, 119.7, 118.8, 111.4, 111.0, 75.0, 61.2, 52.1, 49.4, 46.9, 40.8, 34.2, 31.5, 29.2, 26.4, 23.5, 22.1, 20.8, 16.5. **HRMS (ESI):** m/z calc. for $C_{24}H_{35}N_2O_4$ $[M+H]^+$ 415.2591, found 415.2597.

Methyl (S)-2-((tert-butoxycarbonyl)amino)-3-(2-(1-(((1S,2R,5S)-2-isopropyl-5-methylcyclohexyl)oxy)-1-oxopropan-2-yl)-1H-indol-3-yl)propanoate



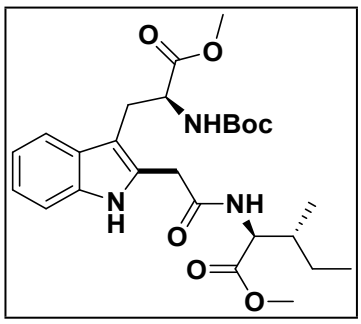
Compound **3f** was prepared according to general procedure **D**, Boc-Trp-OMe (64 mg, 0.20 mmol) and (1*S*,2*R*,5*S*)-2-isopropyl-5-methylcyclohexyl 2-bromopropanoate (29 mg, 0.1 mmol). Flash column chromatography purification (Hexane/ EtOAc 9:1) afforded compound **3f** (25 mg, 47%) as an brown solid.**^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.64 (s, *J*= 75.3 Hz, 1H), 7.48 (d, *J* = 18.2, 7.9 Hz, 1H), 7.30 (t, *J* = 7.2 Hz, 1H), 7.15 (m, 1H), 7.08 (m, 1H), 5.12 (d, *J* = 8.3 Hz, 1H), 4.78 – 4.51 (m, 2H), 3.99 (p, *J* = 6.9 Hz, 1H), 3.63 (s, 3H), 3.25 (m, 2H), 1.93 (dd, *J* = 44.6, 10.6 Hz, 2H), 1.68 (m, 3H), 1.55 (m, 3H), 1.42 (s, 9H), 1.05 (m, 2H), 0.91 (d, *J* = 6.7 Hz, 3H), 0.81 (dd, *J* = 27.3, 6.7 Hz, 6H), 0.57 (dd, *J* = 67.0, 6.7 Hz, 3H).**^{13}C NMR** (100 MHz, $CDCl_3$) δ 174.2, 173.0, 155.4, 135.7, 134.6, 128.3, 122.1, 119.7, 118.7, 111.0, 106.5, 80.0, 75.6, 54.5, 52.4, 47.2, 40.7, 37.3, 34.3, 31.5, 28.4 27.4, 26.4, 25.9, 23.5, 22.1, 20.9, 20.2, 19.1, 16.3. **HRMS (ESI):** m/z calc. for $C_{30}H_{44}N_2NaO_6$ $[M+Na]^+$ 551.3092, found 551.3091.

Methyl (S)-2-((tert-butoxycarbonyl)amino)-3-(2-(2-((1,3-dioxoisoindolin-2-yl)amino)-2-oxoethyl)-1H-indol-3-yl)propanoate



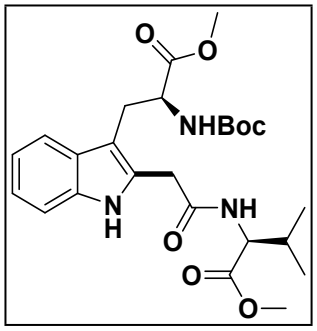
Compound **3h** was prepared according to general procedure **D**, Boc-Trp-OMe (64 mg, 0.20 mmol) and 2-bromo-*N*-(1,3-dioxoisoindolin-2-yl)acetamide (28 mg, 0.10 mmol). Flash column chromatography purification (CH_2Cl_2/ EtOAc 9:1) afforded compound **3h** (21 mg, 40%) as a brown liquid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.43 (s, 1H), 8.74 (s, 1H), 7.86 (m, 2H), 7.75 (m, 2H), 7.46 (d, *J* = 7.7 Hz, 1H), 7.29 (d, *J* = 8.1 Hz, 1H), 7.12 (t, *J* = 7.4 Hz, 1H), 7.07 (t, *J* = 7.4 Hz, 1H), 5.54 (d, *J*= 6.7 Hz, 1H), 4.73 (s, 1H), 3.93 (s, 2H), 3.68 (s, 3H), 3.24 (m, 2H), 1.12 (s, 9H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 172.8, 169.2, 165.2, 155.6, 136.1, 134.9, 134.8, 130.2, 128.6, 127.6, 124.2, 124.1, 122.4, 119.7, 118.7, 111.2, 109.2, 80.5, 54.9, 52.8, 32.5, 28.6, 28.0. **HRMS (ESI):** m/z calc. for $C_{27}H_{28}N_2NaO_7$ $[M+Na]^+$ 543.1850, found 543.1852.

Methyl (2-(3-((S)-2-((tert-butoxycarbonyl)amino)-3-methoxy-3-oxopropyl)-1H-indol-2-yl)acetyl)-L-alloisoleucinate



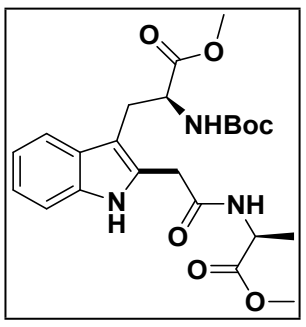
Compound **3i** was prepared according to general procedure **D**, Boc- Trp-OMe (64 mg, 0.20 mmol) and methyl (2-bromoacetyl)-*L*-alloisoleucinate (27 mg, 0.10 mmol). Flash column chromatography purification (Hexane/ EtOAc 8:2) afforded compound **3i** (35 mg, 70%) as a brown liquid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.00 (s, 1H), 7.43 (d, *J* = 7.9 Hz, 1H), 7.28 (d, *J* = 8.0 Hz, 1H), 7.12 (t, *J* = 7.5 Hz, 1H), 7.07 (t, *J* = 7.5 Hz, 1H), 6.91 (s, 1H), 5.36 (s, 1H), 4.53 (m, 2H), 3.72 (m, , 5H), 3.57 (s, 3H), 3.20 (m, 2H), 1.87 (m, 1H), 1.41 (s, 9H), 1.26 (m, 2H), 0.87 (m, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 172.9, 172.4, 170.1, 155.4, 135.9, 129.8, 128.3, 121.9, 119.5, 118.3, 111.1, 107.7, 80.2, 57.2, 55.2, 52.5, 52.2, 37.5, 33.7, 28.4, 28.2, 25.4, 15.6, 11.6. **HRMS (ESI):** m/z calc. for $C_{26}H_{36}N_3NaO_7$ $[M+Na]^+$ 526.2524, found 526.2531.

Methyl (2-(3-((S)-2-((tert-butoxycarbonyl)amino)-3-methoxy-3-oxopropyl)-1H-indol-2-yl)acetyl)-L-valinate



Compound **3j** was prepared according to general procedure **D**, Boc-Trp-OMe (64 mg, 0.20 mmol) and methyl (2-bromoacetyl)-*L*-valinate (25.2 mg, 0.10 mmol). Flash column chromatography purification (CH_2Cl_2/ EtOAc 8:2) afforded compound **3j** (31 mg, 64%) as a brown liquid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.05 (s, 1H), 7.43 (d, *J* = 7.8 Hz, 1H), 7.28 (d, *J* = 8.1 Hz, 1H), 7.11 (t, *J* = 7.5 Hz, 1H), 7.08 – 7.04 (t, *J* = 7.8 Hz, 1H), 6.97 (d, *J* = 6.1 Hz, 1H), 5.39 (s, 1H), 4.50 (m, 2H), 3.86 – 3.63 (m, 5H), 3.57 (s, 3H), 3.18-3.26 (m, 2H), 2.14 (m, 1H), 1.40 (s, 9H), 0.98 – 0.81 (m, 6H).**^{13}C NMR** (100 MHz, $CDCl_3$) δ 172.6, 172.3, 170.1, 155.3 135.7, 129.7, 128.2, 121.8, 119.4, 118.2, 111.0, 107.6, 80.2, 57.8, 55.1, 52.4, 52.2, 33.6, 30.8, 28.2, 28.1, 19.0, 18.0. **HRMS (ESI):** m/z calc. for $C_{25}H_{35}N_3NaO_7$ $[M+Na]^+$ 512.2367, found 512.2358.

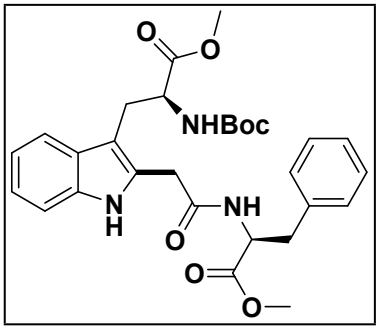
Methyl (S)-2-((tert-butoxycarbonyl)amino)-3-(2-(2-(((S)-1-methoxy-1-oxopropan-2-yl)amino)-2-oxoethyl)-1H-indol-3-yl)propanoate



Compound **3k** was prepared according to general procedure **D**, Boc-Trp-OMe (64 mg, 0.20 mmol) and methyl (2-bromoacetyl)-*L*-alaninate (22.4 mg, 0.10 mmol). Flash column chromatography purification (CH_2Cl_2/ EtOAc 7:3) afforded compound **3k** (32 mg, 69%) as an brown liquid.**^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.86 (s, 1H), 7.44 (d, *J* = 7.9 Hz, 1H), 7.29 (t, *J* = 8.5 Hz, 1H), 7.10 (m, 3H), 5.30

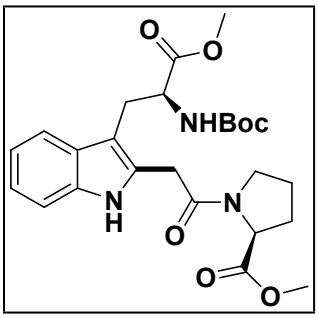
(s, 1H), 4.58 (t, *J* = 7.8 Hz, 1H), 4.52 (m, 1H), 3.83 – 3.64 (m, 5H), 3.62 (s, 3H), 3.21 (m, 2H), 1.38 (d, *J* = 5.9 Hz, 3H), 1.31 (s, 9H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 173.5, 172.8, 170.0, 155.4, 135.9, 129.5, 128.4, 122.0, 119.5, 118.4, 111.1, 108.0, 80.2, 55.1, 52.6, 52.4, 48.5, 33.9, 28.2, 23.0, 17.6. **HRMS (ESI):** m/z calc. for $C_{23}H_{31}N_3NaO_7$ $[M+Na]^+$ 484.2054, found 484.2061.

Methyl (S)-2-((tert-butoxycarbonyl)amino)-3-(2-(2-(((S)-1-methoxy-1-oxo-3-phenylpropan-2-yl)amino)-2-oxoethyl)-1H-indol-3-yl)propanoate



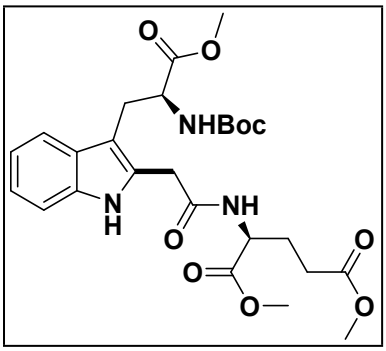
Compound **3l** was prepared according to general procedure **D**, Boc- Trp-OMe (64 mg, 0.20 mmol) and methyl (2-bromoacetyl)-*L*-phenylalaninate (30 mg, 0.10 mmol). Flash column chromatography purification (CH_2Cl_2/ EtOAc 8:2) afforded compound **3l** (37 mg, 69%) as a light brown liquid. **^{1}H NMR** (400 MHz, acetone-d_6) δ 9.88 (s, 1H), 7.46 (d, *J* = 8.8 Hz, 1H), 7.29 (d, *J* = 8.0 Hz, 1H), 7.09 (m, 3H), 7.06 (d, *J* = 2.5 Hz, 2H), 7.04 – 6.99 (m, 1H), 6.95 (t, *J* = 7.4 Hz, 1H), 6.29 (d, *J* = 7.5 Hz, 1H), 4.65 (dd, *J* = 13.5, 7.6 Hz, 1H), 4.40 (dd, *J* = 14.1, 7.9 Hz, 1H), 3.68 (d, *J* = 4.6 Hz, 2H), 3.57 (s, 3H), 3.56 (s, 3H), 3.10 (m, 2H), 3.00 (m, 2H), 1.23 (s, 9H). **^{13}C NMR** (100 MHz, acetone- d_6) δ 173.6, 172.5, 170.0, 156.4, 137.8, 137.0, 131.2, 130.1, 129.2, 127.5, 122.1, 119.7, 119.1, 111.8, 108.8, 79.3, 55.6, 54.7, 52.3, 52.3, 38.0, 34.1, 28.4, 27.7. **HRMS (ESI):** m/z calc. for $C_{29}H_{35}N_3NaO_7$ $[M+Na]^+$ 560.2367, found 560.2369.

Methyl (2-(3-((S)-2-((tert-butoxycarbonyl)amino)-3-methoxy-3-oxopropyl)-1H-indol-2-yl)acetyl)-L-prolinate



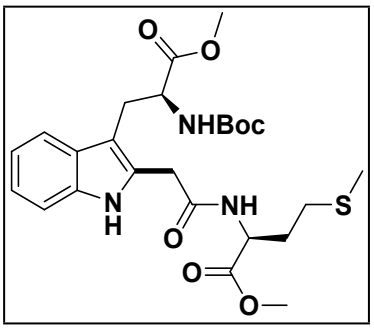
Compound **3m** was prepared according to general procedure **D**, Boc-Trp-OMe (64 mg, 0.20 mmol) and methyl (2-bromoacetyl)-*L*-prolinate (25.0 mg, 0.10 mmol). Flash column chromatography purification (CH_2Cl_2/ EtOAc 7:3) afforded compound **3m** (33 mg, 68%) as a brown liquid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.35 (s, 1H), 7.45 (d, *J* = 8.0 Hz, 1H), 7.30 (d, *J* = 7.9 Hz, 1H), 7.12 (t, *J* = 7.4 Hz, 1H), 7.06 (t, *J* = 7.3 Hz, 1H), 5.29 (s, 1H), 4.58 (m, 1H), 4.53 (dd, *J* = 8.7, 3.3 Hz, 1H), 3.84 (s, 2H), 3.76 (s, 3H), 3.73 – 3.63 (m, 2H), 3.61 (s, 3H), 3.22 (m, 2H), 2.21 (m, 1H), 2.03 (m, 3H), 1.42 (s, 9H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 172.9, 172.9, 169.0, 155.3, 135.8, 129.5, 128.3, 121.8, 119.5, 118.2, 111.2, 106.8, 80.0, 59.1, 54.4, 53.6, 52.6, 47.6, 31.8, 29.3, 28.5, 27.6, 24.9. **HRMS (ESI):** m/z calc. for $C_{25}H_{33}N_3NaO_7$ $[M+Na]^+$ 510.2211, found 510.2206.

Dimethyl (2-(3-((S)-2-((tert-butoxycarbonyl)amino)-3-methoxy-3-oxopropyl)-1H-indol-2-yl)acetyl)-L-glutamate



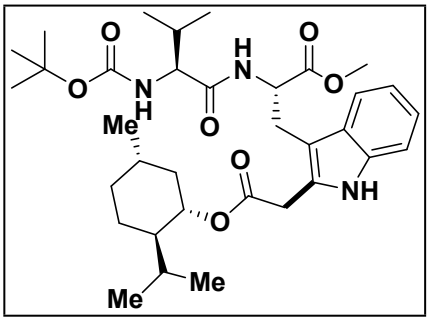
Compound **3n** was prepared according to general procedure **D**, Boc- Trp-OMe (64 mg, 0.20 mmol) and dimethyl (2-bromoacetyl)-*L*-glutamate (29.6 mg, 0.10 mmol). Flash column chromatography purification (CH_2Cl_2/ EtOAc 7:3) afforded compound **3n** (28 mg, 53%) as an brown liquid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.94 (s, 1H), 7.73 (d, *J* = 6.8 Hz, 1H), 7.44 (d, *J* = 7.9 Hz, 1H), 7.29 (d, *J* = 8.1 Hz, 1H), 7.12 (t, *J* = 7.5 Hz, 1H), 7.06 (t, *J* = 7.4 Hz, 1H), 5.40 (d, *J* = 6.6 Hz, 1H), 4.59 (m, 1H), 4.52 (dd, *J* = 13.3, 6.8 Hz, 1H), 3.67-3.76 (m, 5H), 3.62 (s, 3H), 3.59 (s, 3H), 3.27 – 3.10 (m, 2H), 2.37 (t, *J* = 6.1 Hz, 2H), 2.15– 2.25 (m, 1H), 1.92 – 2.02 (m, 1H), 1.30 (s, 9H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 173.3, 172.8, 172.3, 170.4, 155.4, 135.9, 129.4, 128.5, 122.0, 119.5, 118.5, 111.1, 108.1, 80.2, 55.0, 52.7, 52.6, 52.3, 51.9, 33.9, 30.3, 28.4, 28.2, 26.7. **HRMS (ESI):** m/z calc. for $C_{26}H_{35}N_3NaO_9$ $[M+Na]^+$ 556.2266, found 556.2271.

Methyl (2-(3-((S)-2-((tert-butoxycarbonyl)amino)-3-methoxy-3-oxopropyl)-1H-indol-2-yl)acetyl)-L-methioninate



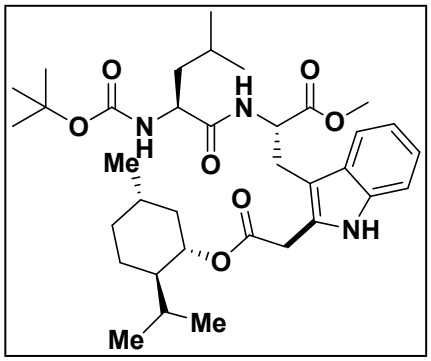
Compound **3o** was prepared according to general procedure **D**, Boc- Trp-OMe (64 mg, 0.20 mmol) and methyl (2-bromoacetyl)-*L*-methioninate (28 mg, 0.10 mmol). Flash column chromatography purification (CH_2Cl_2/ EtOAc 8:2) afforded compound **3o** (11 mg, 21%) as a light brown liquid. **^{1}H NMR** (400 MHz, acetone-d_6) δ 9.95 (s, 1H), 7.60 (t, *J* = 7.0 Hz, 1H), 7.41 (d, *J* = 7.9 Hz, 1H), 7.23 (d, *J* = 7.8 Hz, 1H), 6.94 (t, *J* = 7.4 Hz, 1H), 6.88 (t, *J* = 7.2 Hz, 1H), 6.27 (d, *J* = 8.1 Hz, 1H), 4.53 – 4.44 (m, 1H), 4.36 (q, *J* = 6.2 Hz, 1H), 3.68 (s, 2H), 3.53 (s, 3H), 3.50 (s, 3H), 3.13 (m, 2H), 2.47 – 2.33 (m, 2H), 1.96 (m, 2H), 1.88 (s, 3H), 1.16 (s, 9H). **^{13}C NMR** (100 MHz, acetone- d_6) 173.5, 172.9, 170.2, 156.4, 137.0, 136.9, 129.2, 122.0, 119.6, 119.1, 111.7, 108.7, 79.3, 55.5, 52.4, 52.4, 52.3, 34.0, 32.0, 30.7, 28.4, 27.7, 15.1. **HRMS (ESI):** m/z calc. for $C_{25}H_{35}N_3NaO_7S$ $[M+Na]^+$ 544.2088, found 544.2095.

Methyl (S)-2-((S)-2-((tert-butoxycarbonyl)amino)-3-methylbutanamido)-3-(2-(2-(((1S,2R,5S)-2-isopropyl-5-methylcyclohexyl)oxy)-2-oxoethyl)-1H-indol-3-yl)propanoate



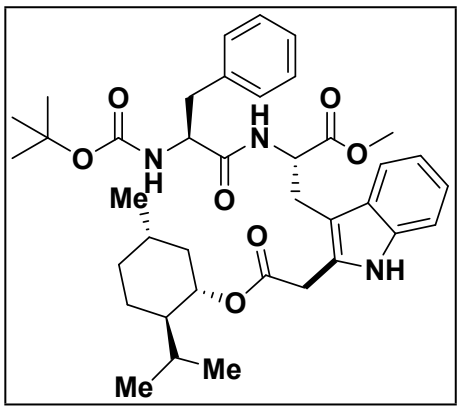
Compound **4b** was prepared according to general procedure **D**, Boc-Val-Trp-OMe (82 mg, 0.30 mmol) and (1*S*,2*R*,5*S*)-2-isopropyl-5-methylcyclohexyl 2-bromoacetate (28 mg, 0.10 mmol). Flash column chromatography purification (CH_2Cl_2/ EtOAc 9:1) afforded compound **4b** (45 mg, 73%) as a yellow solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.70 (s, 1H), 7.50 (d, *J* = 7.8 Hz, 1H), 7.30 (d, *J* = 7.9 Hz, 1H), 7.15 (t, *J* = 7.5 Hz, 1H), 7.10 (t, *J* = 7.4 Hz, 1H), 6.83 (m, 1H), 5.08 (d, *J* = 8.6 Hz, 1H), 4.84 (q, *J* = 6.6 Hz, 1H), 4.76 (td, *J* = 10.9, 4.4 Hz, 1H), 4.02 – 3.90 (m, 1H), 3.76 (s, 2H), 3.62 (s, 3H), 3.23 (d, *J* = 5.7 Hz, 2H), 2.02-2.10 (m, 1H), 1.95-2.01 (m, 2H), 1.85 – 1.75 (m, 1H), 1.68 (d, *J* = 10.9 Hz, 2H), 1.41 (s, 9H), 1.01 (m, 2H), 0.88 (m, 11H), 0.78 (d, *J* = 6.4 Hz, 3H), 0.73 (d, *J* = 6.9 Hz, 3H).**^{13}C NMR** (100 MHz, $CDCl_3$) δ 172.4, 171.7, 170.7, 155.8, 135.8, 128.8, 128.1, 122.3, 119.9, 118.5, 111.1, 107.7, 79.6, 76.0, 59.4, 53.0, 52.4, 47.1, 40.9, 34.2, 32.1, 31.5, 31.0, 29.8, 28.4, 27.0, 26.4, 23.5, 22.1, 20.9, 19.3, 17.3, 16.4. **HRMS (ESI):** m/z calc. for $C_{34}H_{52}N_3O_7$ $[M+H]^+$ 614.3800, found 614.3804.

Methyl (S)-2-((S)-2-((tert-butoxycarbonyl)amino)-4-methylpentanamido)-3-(2-(2-(((1S,2R,5S)-2-isopropyl-5-methylcyclohexyl)oxy)-2-oxoethyl)-1H-indol-3-yl)propanoate



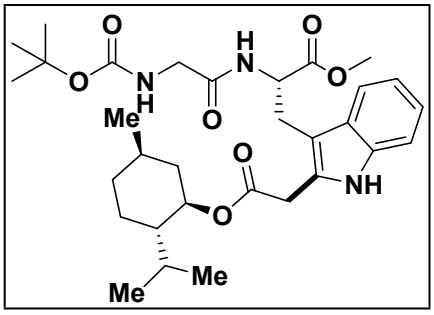
Compound **4c** was prepared according to general procedure **D**, Boc-Leu-Trp-OMe (86 mg, 0.20 mmol) and (1*S*,2*R*,5*S*)-2-isopropyl-5-methylcyclohexyl 2-bromoacetate (28 mg, 0.10 mmol). Flash column chromatography purification (CH_2Cl_2/ EtOAc 8:2) afforded compound **4c** (33 mg, 53%) as a yellow solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.71 (s, 1H), 7.49 (d, *J* = 7.9 Hz, 1H), 7.30 (d, *J* = 7.9 Hz, 1H), 7.15 (t, *J* = 7.5 Hz, 1H), 7.09 (t, *J* = 7.4 Hz, 1H), 6.99 (d, *J* = 7.6 Hz, 1H), 6.88 (s, 1H), 4.85 (q, *J* = 6.4 Hz, 1H), 4.76 (td, *J* = 11.0, 4.4 Hz, 1H), 4.11 (s, 1H), 3.77 (s, 2H), 3.62 (s, 3H), 3.24 (d, *J* = 5.6 Hz, 2H), 1.99 (d, *J* = 11.8 Hz, 2H), 1.89 – 1.74 (m, 2H), 1.68 (d, *J* = 10.8 Hz, 2H), 1.57-1.63 (m, 1H), 1.35-1.48 (m, 3H), 1.38 (s, 9H), 1.09 – 0.93 (m, 2H), 0.88 (m, 14H), 0.74 (t, *J* = 6.2 Hz, 3H).**^{13}C NMR** (100 MHz, $CDCl_3$) δ 172.7, 172.4, 170.7, 155.5, 135.7, 128.8, 128.3, 122.2, 119.8, 118.5, 111.1, 107.7, 79.9, 76.0, 53.0, 52.5, 47.1, 41.8, 40.9, 34.2, 32.1, 31.5, 28.4, 27.1, 26.4, 24.8, 23.5, 23.2, 22.1, 21.9, 20.9, 16.4. **HRMS (ESI):** m/z calc. for $C_{35}H_{54}N_3O_7$ $[M+H]^+$ 628.3956, found 628.3955.

Methyl (S)-2-((S)-2-((tert-butoxycarbonyl)amino)-3-phenylpropanamido)-3-(2-(2-(((1S,2R,5S)-2-isopropyl-5-methylcyclohexyl)oxy)-2-oxoethyl)-1H-indol-3-yl)propanoate



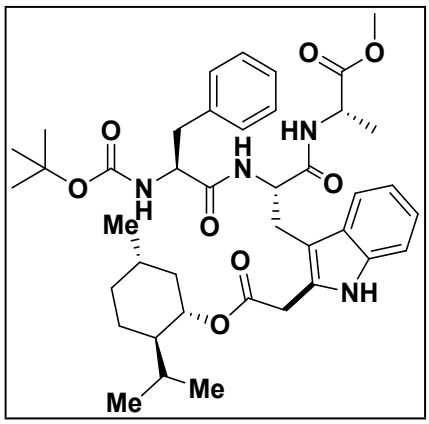
Compound **4d** was prepared according to general procedure **D**, Boc-Phe-Trp-OMe (132 mg, 0.20 mmol) and (1*S*,2*R*,5*S*)-2-isopropyl-5-methylcyclohexyl 2-bromoacetate (28 mg, 0.10 mmol). Flash column chromatography purification (CH_2Cl_2/ EtOAc 9:1) afforded compound **4d** (36 mg, 55%) as a pale yellow liquid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.66 (s, 1H), 7.23 (d, *J* = 8.1 Hz, 1H), 7.20 – 7.15 (m, 2H), 7.13 (d, *J* = 6.4 Hz, 1H), 7.11 – 7.03 (m, 4H), 6.98 (d, *J* = 7.1 Hz, 1H), 6.56 (s, 1H), 4.88 (d, *J*= 7.8 Hz, 1H), 4.76 (q, *J* = 6.5 Hz, 1H), 4.69 (td, *J* = 11.1, 4.4 Hz, 1H), 4.27 (m, 1H), 3.65 (s, 2H), 3.52 (s, 3H), 3.12 (m, 2H), 2.98 (m, 2H), 1.91 (d, *J* = 11.8 Hz, 1H), 1.73 (m, 1H), 1.61 (d, *J* = 11.0 Hz, 2H), 1.36 (m, 1H), 1.26 (s, 9H), 0.95 (m, 2H), 0.79 (m, 8H), 0.67 (t, *J* = 6.7 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 172.1, 171.2, 170.6, 155.2, 136.9, 135.7, 129.5, 128.8, 128.6, 128.2, 126.9, 122.3, 119.9, 118.4, 111.1, 107.5, 80.0, 75.9, 55.6, 53.0, 52.5, 47.1, 40.9, 38.7, 34.2, 32.0, 31.5, 28.3, 27.1, 26.4, 23.5, 22.1, 20.9, 16.4. **HRMS (ESI):** m/z calc. for $C_{38}H_{52}N_3O_7$ $[M+H]^+$ 662.3800, found 662.3798.

Methyl (S)-2-(2-((tert-butoxycarbonyl)amino)acetamido)-3-(2-(2-(((1R,2S,5R)-2-isopropyl-5-methylcyclohexyl)oxy)-2-oxoethyl)-1H-indol-3-yl)propanoate



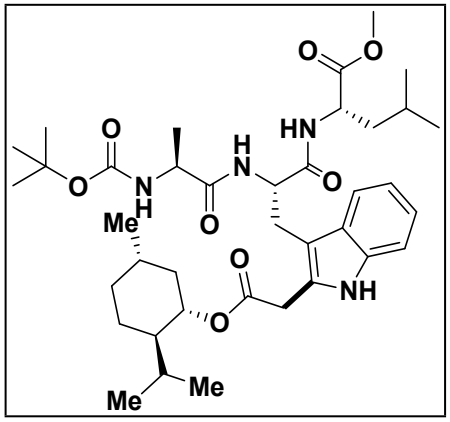
Compound **4e** was prepared according to general procedure **D**, Boc-Gly-Trp-OMe (76 mg, 0.20 mmol) and (1*S*,2*R*,5*S*)-2-isopropyl-5-methylcyclohexyl 2-bromoacetate (28 mg, 0.10 mmol). Flash column chromatography purification (CH_2Cl_2/ EtOAc 8:2) afforded compound **4e** (15 mg, 26%) as a pale brown amorphous solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.74 (s, 1H), 7.46 (d, *J* = 7.9 Hz, 1H), 7.31 (d, *J* = 8.0 Hz, 1H), 7.15 (t, *J* = 7.5 Hz, 1H), 7.09 (t, *J* = 7.4 Hz, 1H), 6.74 (d, *J* = 7.1 Hz, 1H), 5.07 (s, 1H), 4.86 (q, *J* = 6.4 Hz, 1H), 4.76 (td, *J* = 11.1, 4.5 Hz, 1H), 3.73-3.77 (m, 4H), 3.66 (s, 3H), 3.34 – 3.20 (m, 2H), 1.97 (d, *J* = 12.3 Hz, 1H), 1.74-1.83 (m, 1H), 1.69 (d, *J* = 12.5 Hz, 2H), 1.53 – 1.32 (m, 1H), 1.40 (s, 9H), 1.15 – 0.94 (m, 2H), 0.89 (m, 8H), 0.73 (d, *J* = 7.0 Hz, 3H).**^{13}C NMR** (100 MHz, $CDCl_3$) δ 172.2, 170.4, 169.3, 155.8, 135.6, 128.7, 128.0, 122.2, 119.8, 118.2, 111.0, 107.3, 80.0, 75.9, 52.9, 52.5, 47.0, 44.0, 40.8, 34.1, 32.0, 31.0, 28.3, 26.8, 26.3, 23.3, 22.0, 20.8, 16.3. **HRMS (ESI):** m/z calc. for $C_{31}H_{46}N_3O_7$ $[M+H]^+$ 572.3330, found 572.3331.

Methyl ((S)-2-((S)-2-((tert-butoxycarbonyl)amino)-3-phenylpropanamido)-3-(2-(2-(((1S,2R,5S)-2-isopropyl-5-methylcyclohexyl)oxy)-2-oxoethyl)-1H-indol-3-yl)propanoyl)-L-alaninate



Compound **4f** was prepared according to general procedure **D**, Boc-Phe-Trp-Ala-OMe (108 mg, 0.20 mmol) and (1*S*,2*R*,5*S*)-2-isopropyl-5-methylcyclohexyl 2-bromoacetate (28 mg, 0.10 mmol). Flash column chromatography purification (EtOAc/ Hexane 1:1) afforded compound **4f** (28 mg, 38%) as a yellow solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.70 (s, 1H), 7.34 – 7.24 (m, 4H), 7.21 – 7.07 (m, 4H), 6.99 (d, *J* = 8.5 Hz, 1H), 6.75 (d, *J* = 7.4 Hz, 1H), 6.47 (s, 1H), 4.83 – 4.71 (m, 2H), 4.66 (d, *J* = 5.1 Hz, 1H), 4.36 – 4.24 (m, 2H), 3.81 (d, *J* = 3.7 Hz, 2H), 3.59 (s, 3H), 3.15 – 2.88 (m, 4H), 2.02 – 1.94 (m, 1H), 1.87 (dt, *J* = 7.0, 3.5 Hz, 1H), 1.72 – 1.63 (m, 2H), 1.53 – 1.40 (m, 1H), 1.27 – 1.14 (m, 12H), 1.10 – 0.96 (m, 2H), 0.95 – 0.83 (m, 8H), 0.75 (d, *J* = 7.0 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 172.4, 171.0, 171.0, 170.6, 155.5, 136.5, 135.8, 129.5, 129.2, 128.9, 128.2, 127.4, 122.2, 120.0, 118.3, 111.1, 107.8, 80.4, 75.8, 55.9, 53.8, 52.4, 48.4, 47.1, 41.0, 38.0, 34.3, 31.9, 31.6, 28.4, 28.1, 26.3, 23.4, 22.1, 20.9, 18.1, 16.4; **HRMS (ESI):** m/z calc. for $C_{41}H_{57}N_4O_8$ $[M+H]^+$ 733.4171, found 733.4170.

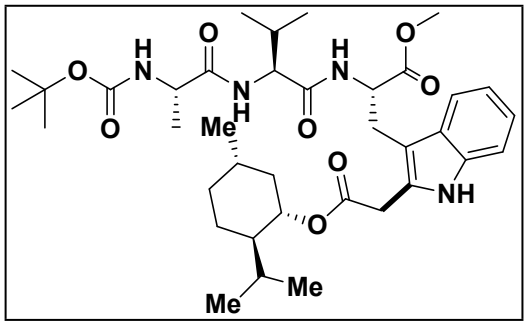
Methyl ((S)-2-((S)-2-((tert-butoxycarbonyl)amino)propanamido)-3-(2-(2-(((1S,2R,5S)-2-isopropyl-5-methylcyclohexyl)oxy)-2-oxoethyl)-1H-indol-3-yl)propanoyl)-L-leucinate



Compound **4g** was prepared according to general **D**, Boc-Ala-Trp-Leu-OMe (100 mg, 0.20 mmol) and (1*S*,2*R*,5*S*)-2-isopropyl-5-methylcyclohexyl 2-bromoacetate (28 mg, 0.10 mmol). Flash column chromatography purification (EtOAc/ Hexane 1:1) afforded compound **4g** (41 mg, 59%) as a brown amorphous solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.69 (s, 1H), 7.51 (d, *J* = 7.8 Hz, 1H), 7.24 (d, *J* = 8.0 Hz, 1H), 7.08 (t, *J* = 7.5 Hz, 1H), 7.01 (t, *J* = 7.4 Hz, 1H), 6.93 (d, *J* = 7.1 Hz, 1H), 6.35 (d, J= 7.1Hz, 1H), 4.89 (d, *J* = 5.7 Hz, 1H), 4.70 (dd, *J* = 10.9, 5.4 Hz, 1H), 4.70 (q, *J* = 6.4 Hz, 1H), 4.38 – 4.24 (m, 1H), 4.05 (t, *J*= 7.2 Hz, 1H), 3.79 (q, *J* = 17.2 Hz, 2H), 3.48 (s, 3H), 3.24 (dd, *J* = 14.2, 5.0 Hz, 1H), 3.03 (dd, *J* = 14.2, 8.3 Hz, 1H), 1.90 (d, *J* = 12.1 Hz, 1H), 1.82 – 1.72 (m, 1H), 1.62 (d, *J* = 11.3 Hz, 2H), 1.38 (m, 4H), 1.29 (s, 9H), 1.21 (d, *J* = 7.0 Hz, 3H), 0.95 (m, 2H), 0.82 (m, 8H), 0.75 (t, *J* = 5.9 Hz, 6H), 0.66 (d, *J* = 6.9 Hz, 3H).**^{13}C NMR** (100 MHz, $CDCl_3$) δ 172.6, 172.4, 171.1, 170.1, 155.4, 135.8, 129.1, 128.1, 122.2, 119.9, 118.5, 111.0, 108.1, 80.1, 75.8, 53.7, 52.2, 51.0,

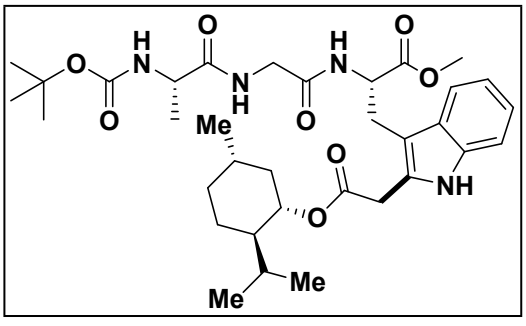
50.5, 47.1, 41.5, 40.9, 34.2, 32.0, 31.5, 28.3, 26.8, 26.3, 24.7, 23.4, 22.7, 22.1, 20.9, 18.6, 16.3; **HRMS (ESI):** m/z calc. for $C_{38}H_{59}N_4O_8$ $[M+H]^+$ 699.4327, found 699.4330.

Methyl (6S,9S,12S)-9-isopropyl-12-((2-(2-(((1S,2R,5S)-2-isopropyl-5-methylcyclohexyl)oxy)-2-oxoethyl)-1H-indol-3-yl)methyl)-2,2,6-trimethyl-4,7,10-trioxo-3-oxa-5,8,11-triazatridecan-13-oate



Compound **4h** was prepared according to general procedure **D**, Boc-Ala-Val-Trp-OMe (98 mg, 0.20 mmol) and (1*S*,2*R*,5*S*)-2-isopropyl-5-methylcyclohexyl 2-bromoacetate (28 mg, 0.10 mmol). Flash column chromatography purification (EtOAc/ Hexane 1:1) afforded compound **4h** (37 mg, 54%) as a brown amorphous solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.63 (s, 1H), 7.50 (d, *J* = 7.8 Hz, 1H), 7.30 (d, *J* = 7.9 Hz, 1H), 7.15 (t, *J* = 7.4 Hz, 1H), 7.09 (t, *J* = 7.4 Hz, 1H), 6.95 (s, 1H), 6.62 (d, *J* = 7.7 Hz, 1H), 5.06 (s, 1H), 4.84 (q, *J* = 6.6 Hz, 1H), 4.77 (td, *J* = 10.9, 4.4 Hz, 1H), 4.31 (dd, *J* = 8.7, 5.6 Hz, 1H), 4.16 – 4.07 (m, 1H), 3.83 – 3.67 (m, 2H), 3.63 (s, 3H), 3.24 (m), 2.12 (m, 1H), 2.03 – 1.96 (m, 1H), 1.89 – 1.76 (m, 1H), 1.68 (d, *J* = 11.3 Hz, 2H), 1.53 – 1.46 (m, 1H), 1.44 – 1.39 (m, 9H), 1.26 (d, *J* = 7.0 Hz, 3H), 1.03 (m, 2H), 0.93 – 0.81 (m, 14H), 0.73 (d, *J* = 6.9 Hz, 3H).**^{13}C NMR** (100 MHz, $CDCl_3$) δ 172.5, 172.3, 171.1, 170.8, 155.5, 135.8, 128.8, 128.0, 122.4, 120.0, 118.5, 111.1, 107.7, 80.1, 76.2, 57.8, 52.0, 52.5, 50.2, 47.1, 40.9, 34.2, 32.2, 31.5, 29.8, 28.4, 27.0, 26.4, 23.5, 22.1, 20.9, 19.3, 18.3, 17.5, 16.4; **HRMS (ESI):** m/z calc. for $C_{37}H_{57}N_4O_8$ $[M+H]^+$ 685.4171, found 685.4165.

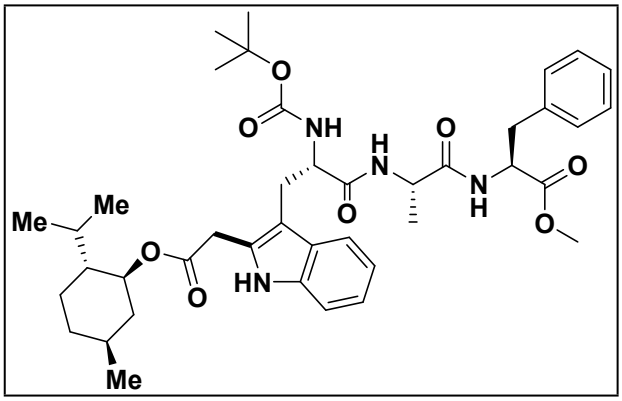
Methyl (6S,12S)-12-((2-(2-(((1S,2R,5S)-2-isopropyl-5-methylcyclohexyl)oxy)-2-oxoethyl)-1H-indol-3-yl)methyl)-2,2,6-trimethyl-4,7,10-trioxo-3-oxa-5,8,11-triazatridecan-13-oate



Compound **4i** was prepared according to general procedure **D**, Boc-Ala-Gly-Trp-OMe (90 mg, 0.20 mmol) and (1*S*,2*R*,5*S*)-2-isopropyl-5-methylcyclohexyl 2-bromoacetate (28 mg, 0.10 mmol). Flash column chromatography purification (EtOAc/ Hexane 1:1) afforded compound **4i** (41 mg, 64%) as a brown amorphous solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.77 (s, 1H), 7.50 (d, *J* = 7.9 Hz, 1H), 7.30 (d, *J* = 7.8 Hz, 1H), 7.15 (t, *J* = 7.5 Hz, 1H), 7.08 (t, *J* = 7.4 Hz, 1H), 6.97 (d, *J* = 7.4 Hz, 1H), 6.54 (d, *J* = 6.5 Hz, 1H), 5.06 (s, 1H), 4.84 (q, *J* = 7.2 Hz, 1H), 4.77 (td, *J* = 10.9, 4.4 Hz, 1H), 4.45 (m, 1H), 3.76 (d, *J* = 4.8 Hz, 2H), 3.73 – 3.69 (m, 1H), 3.67 (s, 3H), 3.60 (m, 1H), 3.24 (m, 2H), 1.97 (d, *J* =

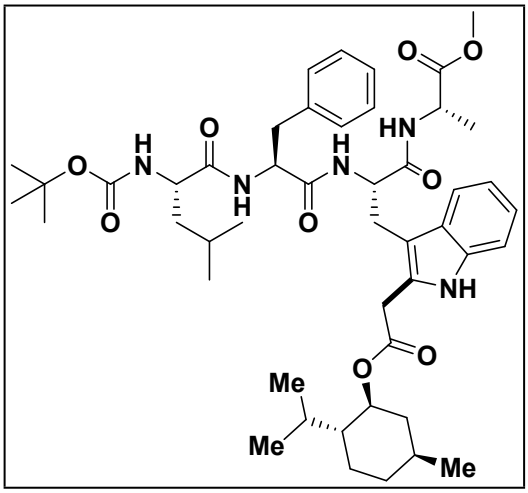
11.8 Hz, 1H), 1.85 – 1.74 (m, 1H), 1.68 (d, *J* = 11.8 Hz, 2H), 1.44 (s, 9H), 1.42-1.37 (m, 1H), 1.27 (d, *J*= 7.0 Hz, 3H), 1.11-0.94 (m, 2H), 0.89 (m, 8H), 0.74 (d, *J* = 6.9 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 172.2, 172.0, 170.6, 168.9, 157.4, 135.6, 128.8, 128.0, 122.1, 120.4, 118.4, 111.0, 107.6, 80.2, 76.0, 52.8, 52.5, 48.4, 47.1, 40.8, 34.1, 32.1, 31.4, 28.3, 26.7, 26.3, 24.2, 23.3, 22.0, 20.8, 18.3, 16.3. **HRMS (ESI):** m/z calc. for $C_{34}H_{51}N_4O_8$ $[M+H]^+$ 643.3701, found 643.3699.

Methyl ((S)-2-((tert-butoxycarbonyl)amino)-3-(2-(2-(((1S,2R,5S)-2-isopropyl-5-methylcyclohexyl)oxy)-2-oxoethyl)-1H-indol-3-yl)propanoyl)-L-alanyl-L-phenylalaninate



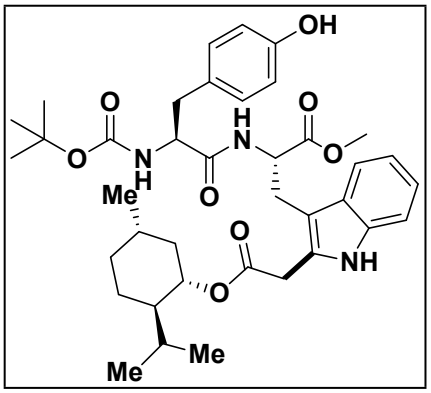
Compound **4j** was prepared according to general procedure **D**, Boc-Trp-Ala-Phe-OMe (108 mg, 0.20 mmol) and (1*S*,2*R*,5*S*)-2-isopropyl-5-methylcyclohexyl 2-bromoacetate (28 mg, 0.10 mmol). Flash column chromatography purification (EtOAc/ Hexane 1:1) afforded compound **4j** (52 mg, 71%) as a brown amorphous solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.66 (s, 1H), 7.48 (d, *J* = 7.8 Hz, 1H), 7.31 – 7.13 (m, 4H), 7.06 (t, *J* = 7.5 Hz, 1H), 6.99 (m, 3H), 6.97 (m, 2H), 5.27 (s, 1H), 4.68 (td, *J* = 10.7, 4.1 Hz, 1H), 4.62 (q, *J* = 7.3 Hz, 1H), 4.36-4.27 (m, 1H), 4.25-4.16 (m, 1H), 3.73 (m, 2H), 3.61 (s, 3H), 3.22-3.01 (m, 2H), 3.00-2.83 (m, 2H), 1.95-1.90 (m, 1H), 1.80 – 1.70 (m, 1H), 1.61 (d, *J* = 11.4 Hz, 2H), 1.44 – 1.35 (m, 1H), 1.33 (s, 9H), 1.05 (d, *J* = 7.0 Hz, 3H), 0.89-1.00 (m, 2H), 0.81 (m, 8H), 0.65 (d, *J* = 6.9 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 171.8, 171.7, 171.3, 170.7, 155.6, 136.0, 135.8, 129.3, 129.0, 128.7, 128.1, 127.2, 122.2, 119.9, 118.6, 111.0, 108.1, 80.2, 75.8, 60.5, 53.5, 52.4, 49.0, 47.1, 40.9, 37.9, 34.2, 32.0, 31.5, 28.4, 26.3, 23.4, 22.1, 20.9, 18.0, 16.3, 14.3; **HRMS (ESI):** m/z calc. for $C_{41}H_{57}N_4O_8$ $[M+H]^+$ 733.4171, found 733.4170.

Methyl ((S)-2-((S)-2-((S)-2-((tert-butoxycarbonyl)amino)-4-methylpentanamido)-3-phenylpropanamido)-3-(2-(2-(((1S,2R,5S)-2-isopropyl-5-methylcyclohexyl)oxy)-2-oxoethyl)-1H-indol-3-yl)propanoyl)-L-alaninate



Compound **4k** was prepared according to general procedure **D**, Boc-Leu-Phe-Trp-Ala-OMe (169 mg, 0.20 mmol) and (1*S*,2*R*,5*S*)-2-isopropyl-5-methylcyclohexyl 2-bromoacetate (28 mg, 0.10 mmol). Flash column chromatography purification (EtOAc/ Hexane 1:1) afforded compound **4k** (55 mg, 65%) as an yellow solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.66 (s, 1H), 7.35 (d, *J* = 7.7 Hz, 1H), 7.28 – 7.12 (m, 5H), 7.09 – 7.03 (m, 1H), 6.98 (t, *J* = 7.4 Hz, 1H), 6.76 (d, *J* = 7.4 Hz, 1H), 6.65 (d, *J* = 6.4 Hz, 1H), 6.42 (d, *J* = 5.2 Hz, 1H), 4.76 – 4.62 (m, 2H), 4.55 (m, 2H), 4.30 – 4.18 (m, 2H), 3.72 (m, 1H), 3.51 (s, 3H), 3.15 - 2.97 (m, 2H), 2.96 – 2.74 (m, 2H), 1.91 (m, 2H), 1.77 (m, 1H), 1.61 (d, *J* = 11.3 Hz, 2H), 1.37 (s, 9H), 1.34 – 1.25 (m, 1H), 1.20 – 1.12 (m, 5H), 1.05 – 0.89 (m, 2H), 0.83-0.80 (m, 8H), 0.77 (dd, J= 9.7, 6.6 Hz, 6H), 0.65 (d, *J* = 6.7 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 172.7, 172.5, 171.0, 170.5, 170.4, 155.9, 136.5, 135.8, 129.4, 129.0, 128.9, 128.7, 128.2, 127.2, 122.1, 119.8, 118.5, 111.0, 108.2, 80.4, 75.8, 54.5, 53.7, 53.3, 52.4, 48.3, 47.1, 40.9, 38.1, 34.2, 31.9, 31.5, 28.5, 28.1, 27.0, 26.3, 24.8, 23.4, 23.1, 22.1, 21.9, 20.9, 18.1, 16.4. **HRMS (ESI):** m/z calc. for $C_{47}H_{68}N_5O_9$ $[M+H]^+$ 846.5012, found 846.5003.

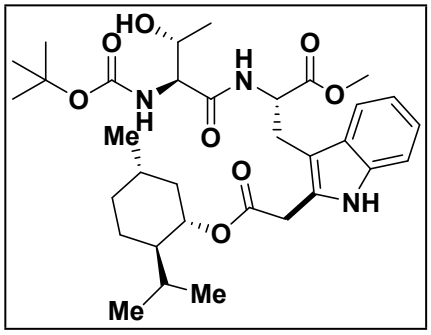
Methyl (S)-2-((S)-2-((tert-butoxycarbonyl)amino)-3-(4-hydroxyphenyl)propanamido)-3-(2-(2-(((1S,2R,5S)-2-isopropyl-5-methylcyclohexyl)oxy)-2-oxoethyl)-1H-indol-3-yl)propanoate



Compound **4l** was prepared according to general procedure **D**, Boc-Tyr-Trp-OMe (136 mg, 0.20 mmol) and (1*S*,2*R*,5*S*)-2-isopropyl-5-methylcyclohexyl 2-bromoacetate (28 mg, 0.10 mmol). Flash column chromatography purification (CH_2Cl_2/ EtOAc 8:2) afforded compound **4l** (37 mg, 55%) as a pale yellow liquid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.78 (s, 1H), 7.35 (d, *J* = 6.7 Hz, 1H), 7.29 (d, *J* = 8.0 Hz, 1H), 7.14 (t, *J* = 7.5 Hz, 1H), 7.06 (m, 1H), 6.92 (d, *J*= 6.8 Hz, 2H), 6.62 (m, 3H), 5.07 (d, *J* = 7.7 Hz, 1H), 4.88 – 4.64 (m, 2H), 4.29 (m, 1H), 3.69 (s, 2H), 3.59 (s, 3H), 3.19 (s, 2H), 2.86 – 2.69 (m, 2H), 1.94-1.86 (m, 1H), 1.84 – 1.73 (m, 1H), 1.67 (d, *J* = 11.2 Hz, 2H), 1.48 – 1.39 (m, 1H), 1.36 (s, 9H), 1.11 – 0.93 (m, 2H), 0.94 – 0.76 (m, 8H), 0.71 (d, *J* = 6.8 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 172.1, 171.5, 170.7, 155.4, 155.2, 135.7, 130.5, 128.8, 128.2, 128.1, 122.3, 119.9, 118.4, 115.6,

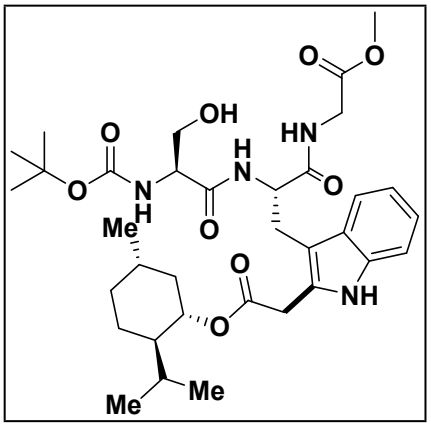
111.1, 107.4, 80.2, 76.0, 55.9, 53.0, 52.6, 47.1, 40.9, 37.9, 34.2, 32.0, 31.5, 28.4, 27.0, 26.4, 23.4, 22.1, 20.9, 16.4. **HRMS (ESI):** m/z calc. for $C_{38}H_{52}N_3O_8$ $[M+H]^+$ 678.3749, found 678.3746.

Methyl (S)-2-((2S,3R)-2-((tert-butoxycarbonyl)amino)-3-hydroxybutanamido)-3-(2-(2-(((1S,2R,5S)-2-isopropyl-5-methylcyclohexyl)oxy)-2-oxoethyl)-1H-indol-3-yl)propanoate



Compound **4m** was prepared according to general procedure **D**, Boc-Thr-Trp-OMe (82 mg, 0.20 mmol) and (1*S*,2*R*,5*S*)-2-isopropyl-5-methylcyclohexyl 2-bromoacetate (28 mg, 0.10 mmol). Flash column chromatography purification (CH_2Cl_2/ EtOAc 8:2) afforded compound **4m** (32 mg, 51%) as a pale brown amorphous solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.74 (s, 1H), 7.50 (d, *J* = 7.8 Hz, 1H), 7.31 (d, *J* = 8.0 Hz, 1H), 7.19 – 7.13 (m, 2H), 7.10 (t, *J* = 7.4 Hz, 1H), 5.35 (d, *J* = 7.7 Hz, 1H), 4.84 (q, *J* = 6.5 Hz, 1H), 4.76 (td, *J* = 10.8, 4.3 Hz, 1H), 4.30 - 4.20 (m, 1H), 4.06 (d, *J* = 7.7 Hz, 1H), 3.77 (s, 2H), 3.66 (s, 3H), 3.24 (m, 2H), 1.99 (d, *J* = 12.2 Hz, 1H), 1.86 – 1.73 (m, 1H), 1.68 (d, *J* = 11.0 Hz, 2H), 1.51 – 1.45 (m, 1H), 1.40 (s, 9H), 1.11 (d, *J* = 6.4 Hz, 3H), 1.09 – 0.96 (m, 2H), 0.88 (dd, *J* = 10.0, 6.8 Hz, 8H), 0.73 (d, *J* = 6.9 Hz, 3H).**^{13}C NMR** (100 MHz, $CDCl_3$) δ 172.4, 171.3, 170.6, 156.2, 135.7, 128.8, 128.1, 122.3, 119.9, 118.4, 111.1, 107.5, 80.2, 76.0, 67.5, 58.5, 53.1, 52.6, 47.1, 40.9, 34.2, 32.1, 31.5, 28.4, 26.9, 26.4, 23.5, 22.1, 20.9, 18.3, 16.4. **HRMS (ESI):** m/z calc. for $C_{33}H_{50}N_3O_8$ $[M+H]^+$ 616.3592, found 616.3593.

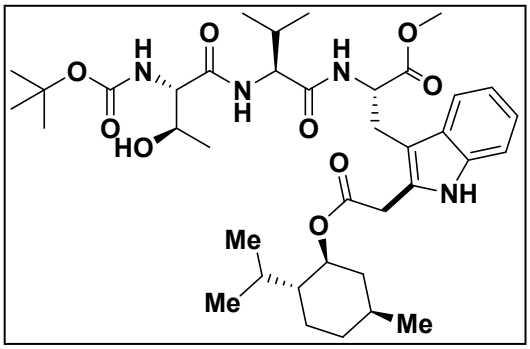
Methyl (6S,9S)-6-(hydroxymethyl)-9-((2-(2-(((1S,2R,5S)-2-isopropyl-5-methylcyclohexyl)oxy)-2-oxoethyl)-1H-indol-3-yl)methyl)-2,2-dimethyl-4,7,10-trioxo-3-oxa-5,8,11-triazatridecan-13-oate



Compound **4n** was prepared according to general procedure **D**, Boc-Ser-Trp-Gly-OMe (92 mg, 0.20 mmol) and (1*S*,2*R*,5*S*)-2-isopropyl-5-methylcyclohexyl 2-bromoacetate (28 mg, 0.10 mmol). Flash column chromatography purification (EtOAc/ Hexane 1:1) afforded compound **4n** (34 mg, 51%) as a brown amorphous solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.68 (s, 1H), 7.57 (d, *J* = 7.7 Hz, 1H), 7.31 (d, *J* = 7.9 Hz, 1H), 7.21 (d, *J* = 7.5 Hz, 1H), 7.15 (t, *J* = 7.5 Hz, 1H), 7.09 (t, *J* = 7.4 Hz, 1H), 6.83 (s, 1H), 5.42 (d, *J* = 5.3 Hz, 1H), 4.81 – 4.72 (m, 2H), 4.14 (d, *J* = 3.5 Hz, 1H), 3.91 (m, 2H), 3.83 (d, *J* = 9.6 Hz, 1H), 3.75 (dd, *J* = 18.7, 6.1 Hz, 1H), 3.62 (s, 3H), 3.62 – 3.58 (m, 1H), 3.37 – 3.15 (m, 2H), 3.03 (s, 1H), 1.97 (d, *J* = 11.9 Hz, 1H), 1.91 – 1.78 (m, 1H), 1.69 (d, *J* = 11.5 Hz, 2H), 1.56 – 1.44 (m, 1H), 1.36 (s, 9H), 1.12 – 0.93 (m, 2H), 0.94 – 0.82 (m, 8H), 0.74 (d, *J* = 6.9 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 171.7, 171.2, 171.1, 170.1, 155.9, 135.8,

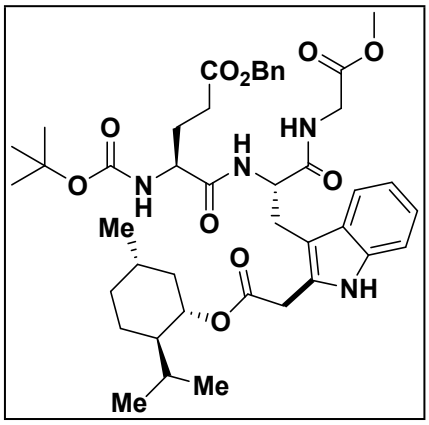
129.2, 128.1, 122.4, 120.0, 118.5, 111.1, 108.0, 80.4, 76.0, 63.3, 55.8, 53.8, 52.4, 47.1, 41.4, 40.9, 34.2, 32.1, 31.5, 28.3, 27.0, 26.4, 23.4, 22.1, 20.9, 16.4; **HRMS (ESI):** m/z calc. for $C_{34}H_{51}N_4O_9$ $[M+H]^+$ 659.3651, found 659.3649.

Methyl (6S,9S,12S)-6-((R)-1-hydroxyethyl)-9-isopropyl-12-((2-(2-(((1S,2R,5S)-2-isopropyl-5-methylcyclohexyl)oxy)-2-oxoethyl)-1H-indol-3-yl)methyl)-2,2-dimethyl-4,7,10-trioxo-3-oxa-5,8,11-triazatridecan-13-oate



Compound **4o** was prepared according to general procedure **D**, Boc-Thr-Val-Trp-OMe (104 mg, 0.20 mmol) and (1*S*,2*R*,5*S*)-2-isopropyl-5-methylcyclohexyl 2-bromoacetate (28 mg, 0.10 mmol). Flash column chromatography purification (CH_2Cl_2/ EtOAc 8:2) afforded compound **4o** (48 mg, 67%) as an yellow powder. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.58 (s, 1H), 7.44 (d, *J* = 7.9 Hz, 1H), 7.24 (d, *J* = 8.0 Hz, 1H), 7.09 (t, *J* = 7.5 Hz, 1H), 7.03 (m, 2H), 6.79 (d, *J* = 8.9 Hz, 1H), 5.40 (d, *J* = 8.0 Hz, 1H), 4.80 (dd, *J* = 13.3, 6.6 Hz, 1H), 4.70 (td, *J* = 10.8, 4.3 Hz, 1H), 4.22 (dd, *J* = 8.7, 5.6 Hz, 1H), 4.07 (m, 1H), 3.95 (d, *J* = 7.9 Hz, 1H), 3.70 (s, 2H), 3.57 (s, 3H), 3.24 – 3.08 (m, 2H), 2.08 (m, 2H), 1.93 (d, *J* = 11.6 Hz, 1H), 1.74 (m, 1H), 1.62 (d, *J* = 10.9 Hz, 2H), 1.37 (s, 9H), 1.18 (m, 1H), 1.02 (d, *J* = 6.4 Hz, 3H), 0.98 – 0.88 (m, 2H), 0.82 (m, 11H), 0.75 (d, *J* = 6.7 Hz, 3H), 0.67 (d, *J* = 6.9 Hz, 3H).**^{13}C NMR** (101 MHz, $CDCl_3$) δ 172.4, 171.7, 171.1, 170.9, 156.3, 135.8, 128.8, 128.0, 122.4, 120.0, 118.5, 111.0, 107.7, 80.3, 76.2, 67.0, 58.2, 57.7, 52.9, 52.5, 47.1, 40.9, 34.2, 32.2, 31.5, 30.9, 28.4, 26.9, 26.4, 23.4, 22.1, 20.9, 19.4, 18.2, 17.4, 16.4. **HRMS (ESI):** m/z calc. for $C_{38}H_{59}N_4O_9$ $[M+H]^+$ 715.4277, found 715.4275.

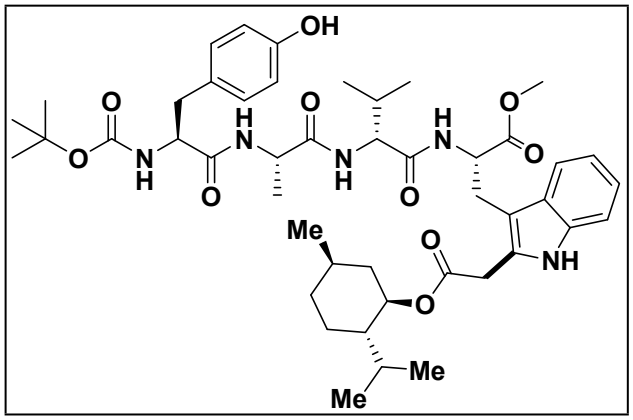
Methyl (6S,9S)-6-(3-(benzyloxy)-3-oxopropyl)-9-((2-(2-(((1S,2R,5S)-2-isopropyl-5-methylcyclohexyl)oxy)-2-oxoethyl)-1H-indol-3-yl)methyl)-2,2-dimethyl-4,7,10-trioxo-3-oxa-5,8,11-triazatridecan-13-oate



Compound **4p** was prepared according to general procedure **D**, Boc-Glu(OBn)-Trp-Gly-OMe (158 mg, 0.20 mmol) and (1*S*,2*R*,5*S*)-2-isopropyl-5-methylcyclohexyl 2-bromoacetate (28 mg, 0.10 mmol). Preparative HPLC isolation (H_2O:MeOH:MeCN/60:30:10) afforded compound **4p** (50 mg, 50%) as a light brown liquid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.63 (s, 1H), 7.49 (d, *J* = 7.5 Hz, 1H), 7.30 – 7.22 (m, 5H), 7.20 (d, *J* = 8.2 Hz, 1H), 7.11 – 6.97 (m, 3H), 6.59 (s, 1H), 5.23 (d, *J* = 3.7 Hz, 1H), 5.03

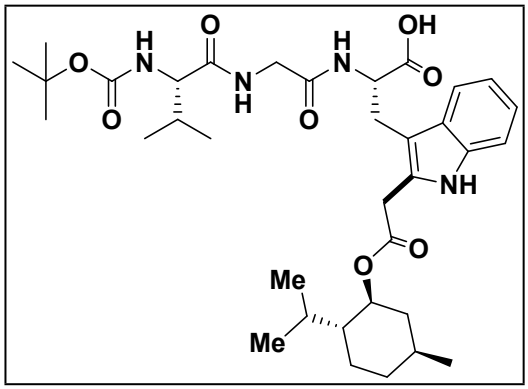
(s, 2H), 4.73 – 4.62 (m, 2H), 4.00 (q, *J* = 6.5 Hz, 1H), 3.84 – 3.80 (m, 2H), 3.66 – 3.59 (m, 1H), 3.53 (s, 3H), 3.27 – 3.04 (m, 2H), 2.28 (t, *J* = 7.2 Hz, 2H), 2.02 – 1.87 (m, 2H), 1.84 – 1.74 (m, 2H), 1.61 (d, *J* = 11.4 Hz, 2H), 1.45 – 1.30 (m, 1H), 1.26 (s, 9H), 1.05 – 0.87 (m, 2H), 0.88 – 0.74 (m, 8H), 0.66 (d, *J* = 6.9 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 173.2, 171.5, 171.4, 171.1, 169.6, 155.8, 135.8, 135.7, 129.2, 128.7, 128.4, 128.4, 128.1, 122.2, 120.0, 118.4, 111.1, 108.0, 80.3, 75.8, 66.7, 54.6, 53.6, 52.2, 47.1, 41.3, 40.9, 34.2, 31.9, 31.5, 30.5, 28.3, 27.0, 26.3, 23.4, 22.1, 20.9, 16.3. **HRMS (ESI):** m/z calc. for $C_{39}H_{51}N_5NaO_{11}$ $[M+Na]^+$ 788.3477, found 788.3480.

Methyl (6S,9S,12R,15S)-6-(4-hydroxybenzyl)-12-isopropyl-15-((2-(2-(((1S,2R,5S)-2-isopropyl-5-methylcyclohexyl)oxy)-2-oxoethyl)-1H-indol-3-yl)methyl)-2,2,9-trimethyl-4,7,10,13-tetraoxo-3-oxa-5,8,11,14-tetraazahexadecan-16-oate



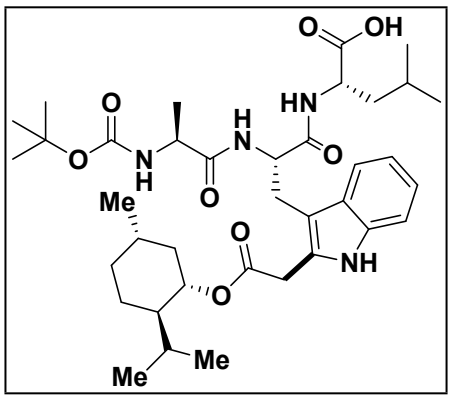
Compound **4q** was prepared according to general procedure **D**, Boc-Tyr-Ala-Val-Trp-OMe (130 mg, 0.20 mmol) and (1*S*,2*R*,5*S*)-2-isopropyl-5-methylcyclohexyl 2-bromoacetate (28 mg, 0.10 mmol). Flash column chromatography purification (EtOAc/Hexane 1:1) afforded compound **4q** (37 mg, 44%) as a yellow solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.72 (s, 1H), 7.52 - 7.44 (m, 2H), 7.29 (d, *J* = 8.0 Hz, 1H), 7.14 (t, *J* = 7.0 Hz, 1H), 7.07 (t, *J* = 7.1 Hz, 1H), 6.96 (m, 3H), 6.69 (d, *J* = 8.4 Hz, 2H), 6.63 (d, *J* = 8.3 Hz, 1H), 5.14 (d, *J* = 7.6 Hz, 1H), 4.85 (q, *J* = 6.8 Hz, 1H), 4.75 (td, *J* = 10.9, 4.3 Hz, 1H), 4.35 (t, *J* = 6.8 Hz, 1H), 4.31 – 4.26 (m, 2H), 3.74 (s, 2H), 3.64 (s, 3H), 3.31 – 3.15 (m, 2H), 2.93 (d, *J* = 6.3 Hz, 2H), 2.09 (m, 1H), 1.97 (d, *J* = 11.7 Hz, 1H), 1.83 – 1.74 (m, 1H), 1.67 (d, *J* = 11.2 Hz, 2H), 1.48 (m, 1H), 1.40 (s, 9H), 1.18 (d, *J* = 7.0 Hz, 3H), 1.00 (m, 2H), 0.92 – 0.79 (m, 14H), 0.71 (d, *J* = 6.9 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 172.4, 172.0, 171.5, 171.2, 170.9, 157.7, 155.5, 136.9, 135.8, 130.5, 128.8, 128.0, 127.8, 122.4, 120.5, 120.0, 118.5, 115.9, 111.1, 107.7, 80.4, 76.2, 58.2, 56.0, 53.0, 52.5, 49.3, 47.1, 40.9, 37.7, 34.2, 32.3, 31.5, 28.4, 26.9, 26.4, 24.4, 23.5, 22.1, 20.9, 19.3, 18.4, 17.8, 16.4; **HRMS (ESI):** m/z calc. for $C_{46}H_{66}N_5O_{10}$ $[M+H]^+$ 848.4804, found 848.4801.

(6S,12S)-6-isopropyl-12-((2-(2-(((1S,2R,5S)-2-isopropyl-5-methylcyclohexyl)oxy)-2-oxoethyl)-1H-indol-3-yl)methyl)-2,2-dimethyl-4,7,10-trioxo-3-oxa-5,8,11-triazatridecan-13-oic acid



Compound **4r** was prepared according to general procedure **D**, Boc-Val-Ala-Trp-OH (131 mg, 0.20 mmol) and (1*S*,2*R*,5*S*)-2-isopropyl-5-methylcyclohexyl 2-bromoacetate (28 mg, 0.10 mmol). Flash column chromatography purification (EtOAc/ Hexane 1:1) afforded compound **4r** (46 mg, 70%) as a yellow powder. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.76 (s, 1H), 7.41 (d, *J* = 7.8 Hz, 1H), 7.22 (d, *J* = 8.0 Hz, 1H), 7.07 (t, *J* = 7.4 Hz, 1H), 7.00 (t, *J* = 7.3 Hz, 1H), 6.90 (d, *J* = 7.4 Hz, 1H), 6.71 (s, 1H), 5.04 (d, *J* = 6.2 Hz, 1H), 4.82 – 4.62 (m, 2H), 4.08 – 3.93 (m, 1H), 3.86 – 3.69 (m, 2H), 3.68 (s, 2H), 3.24 – 3.08 (m, 2H), 1.90 (d, *J* = 11.9 Hz, 1H), 1.80 – 1.68 (m, 1H), 1.61 (d, *J* = 11.6 Hz, 2H), 1.48 – 1.40 (m, 1H), 1.36 (s, 9H), 1.19 (d, J = 6.5 Hz, 3H), 1.07 (t, *J* = 7.1 Hz,3H), 1.03 – 0.88 (m, 3H), 0.86 – 0.74 (m, 8H), 0.66 (d, *J* = 6.9 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 173.0, 171.9, 170.7, 168.7, 155.6, 135.7, 128.8, 128.1, 122.2, 119.8, 118.4, 111.1, 107.6, 80.2, 75.9, 61.7, 53.1, 47.1, 42.7, 40.9, 34.2, 32.1, 31.5, 28.4, 27.0, 26.8, 26.4, 23.4, 22.1, 20.9, 18.6, 16.4, 14.0. HRMS (ESI): m/z calc. for $C_{35}H_{53}N_4O_8$ [M+H]+ 657.3858, found 657.3853.

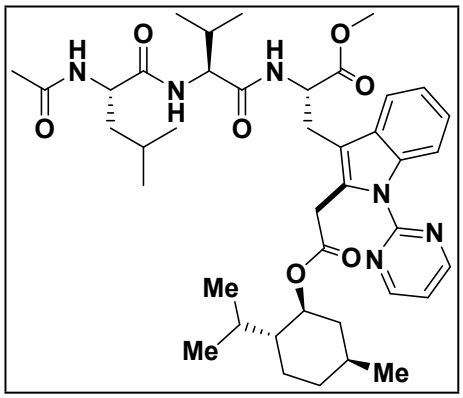
((S)-2-((S)-2-((tert-butoxycarbonyl)amino)propanamido)-3-(2-(2-(((1S,2R,5S)-2-isopropyl-5-methylcyclohexyl)oxy)-2-oxoethyl)-1H-indol-3-yl)propanoyl)-L-leucine



Compound **4s** was prepared according to general procedure **D**, Boc-Ala-Trp-Leu-OH (149 mg, 0.20 mmol) and (1*S*,2*R*,5*S*)-2-isopropyl-5-methylcyclohexyl 2-bromoacetate (28 mg, 0.10 mmol). Flash column chromatography purification (EtOAc/ Hexane 1:1) afforded compound **4s** (35 mg, 55%) as a yellow powder. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (s, 1H), 7.70 (d, *J* = 7.8 Hz, 1H), 7.36 (d, *J* = 8.0 Hz, 1H), 7.20 (t, *J* = 7.5 Hz, 1H), 7.14 (d, *J* = 7.5 Hz, 1H), 7.11 (t, *J* = 2.0 Hz, 1H), 6.97 (d, *J* = 7.6 Hz, 1H), 6.92 (d, *J* = 7.8 Hz, 1H), 6.47 (d, *J* = 7.8 Hz, 1H), 5.00 (d, *J* = 6.7 Hz, 1H), 4.80 – 4.73 (m, 2H), 4.69 – 4.43 (m, 3H), 4.22 – 4.07 (m, 1H), 3.40 – 3.15 (m, 2H), 2.05 – 1.95 (m, 1H), 1.95 – 1.79 (m, 1H), 1.74 – 1.55 (m, 3H), 1.58 – 1.39 (m, 3H), 1.37 (s, 9H), 1.35 – 1.23 (m, 4H), 1.10 – 0.92 (m, 3H), 0.93 – 0.86 (m, 12H), 0.77 (d, *J* = 6.9 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 172.6, 171.8, 171.1, 167.2, 155.5, 136.3, 127.6, 123.8, 122.3, 119.8, 118.9, 111.4, 110.3, 80.3, 75.9, 61.2, 53.8, 50.9,

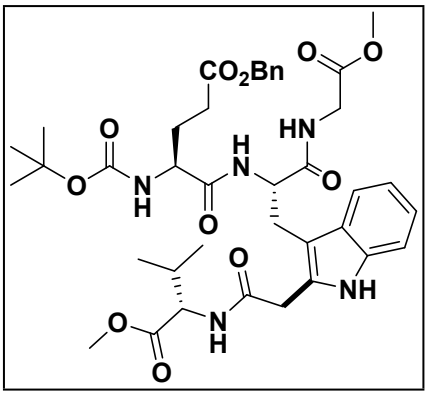
47.0, 41.2, 40.8, 34.2, 31.5, 28.3, 28.3, 27.9, 26.3, 24.6, 23.4, 22.9, 22.1, 21.8, 20.8, 18.4, 16.4, 14.3.

Methyl (S)-2-((S)-2-((S)-2-acetamido-4-methylpentanamido)-3-methylbutanamido)-3-(2-(2-(((1S,2R,5S)-2-isopropyl-5-methylcyclohexyl)oxy)-2-oxoethyl)-1-(pyrimidin-2-yl)-1H-indol-3-yl)propanoate



Compound **4t** was prepared according to general procedure **D**, Ac-Leu-Val-Trp-OMe (149 mg, 0.20 mmol) and (1*S*,2*R*,5*S*)-2-isopropyl-5-methylcyclohexyl 2-bromoacetate (28 mg, 0.10 mmol). Flash column chromatography purification (EtOAc/ Hexane 1:1) afforded compound **4t** (40 mg, 54%) as a white powder. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.66 (d, *J* = 4.8 Hz, 2H), 8.42 (d, *J* = 8.3 Hz, 1H), 7.76 (d, *J* = 4.9 Hz, 1H), 7.54 (d, *J* = 7.7 Hz, 1H), 7.25 (t, *J* = 7.7 Hz, 1H), 7.19 (t, *J* = 7.5 Hz, 1H), 7.08 (t, *J* = 4.8 Hz, 1H), 6.50 (d, *J* = 8.7 Hz, 1H), 6.09 (d, *J* = 8.3 Hz, 1H), 4.64 - 4.76 (m, 2H), 4.33 – 4.42 (m, 2H), 4.09 – 3.81 (m, 2H), 3.66 (s, 3H), 3.31 (dd, *J* = 14.5, 4.9 Hz, 1H), 3.00 (dd, *J* = 14.5, 10.0 Hz, 1H), 2.15 – 1.97 (m, 2H), 1.87 (s, 3H), 1.86 – 1.75 (m, 2H), 1.69 – 1.58 (m, 2H), 1.52 – 1.28 (m, 5H), 1.06 – 0.90 (m, 2H), 0.88 – 0.81 (m, 9H), 0.74 – 0.79 (m, 9H), 0.70 (d, *J* = 6.9 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 172.6, 172.0, 171.7, 169.9, 158.0, 157.9, 136.4, 130.6, 128.6, 124.34122.4, 118.5, 117.0, 115.1, 115.0, 75.9, 57.1, 52.9, 52.5, 51.9, 47.1, 42.0, 41.2, 34.4, 33.7, 32.6, 31.5, 26.9, 26.4, 24.8, 23.6, 23.3, 23.0, 22.3, 22.2, 20.9, 19.7, 16.7, 16.4. HRMS (ESI): m/z calc. for $C_{41}H_{59}N_6O_7$ [M+H]+ 747.4440, found 747.4439.

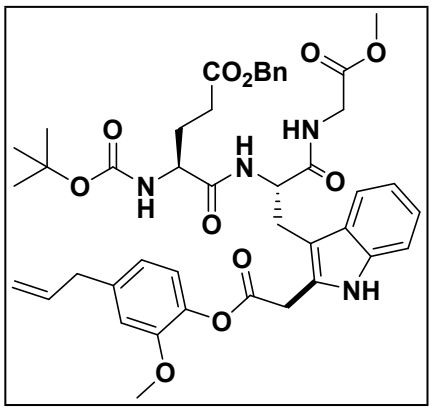
Methyl (6S,9S)-6-(3-(benzyloxy)-3-oxopropyl)-9-((2-(2-(((S)-1-methoxy-3-methyl-1-oxobutan-2-yl)amino)-2-oxoethyl)-1H-indol-3-yl)methyl)-2,2-dimethyl-4,7,10-trioxo-3-oxa-5,8,11-triazatridecan-13-oate



Compound **4u** was prepared according to general procedure **D**, Boc-Glu(OBn)-Trp-Gly-OMe (158 mg, 0.20 mmol) and methyl (2-bromoacetyl)-*L*-valinate (25 mg, 0.10 mmol). Preparative HPLC isolation (H_2O:MeOH:MeCN/60:30:10) afforded compound **4u** (50 mg, 50%) as an light brown liquid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.13 (s, 1H), 7.50 (d, *J* = 7.6 Hz, 1H), 7.42 (d, *J*= 7.4, 1H), 7.37 – 7.31 (m, 5H), 7.10 (t, *J* = 7.4 Hz, 1H), 7.05 (t, *J* = 7.3 Hz, 1H), 6.76 (s, 1H), 5.40 (d, *J* = 6.4 Hz, 1H), 5.09 (s, 2H), 4.73 (q, *J* = 7.2 Hz, 1H), 4.51 (dd, *J* = 8.2, 5.3 Hz, 1H), 4.12 (q, *J* = 7.4 Hz, 1H), 3.83 (s, 2H), 3.69 (s, 3H), 3.60 (s, 3H), 3.48 (s, 2H), 3.32 – 3.16 (m, 2H), 2.36 (t, *J* = 7.2 Hz, 2H), 2.17 (m, 2H), 1.80-1.90 (m, 1H), 1.35 (s, 9H), 0.93 (t, *J* = 6.8

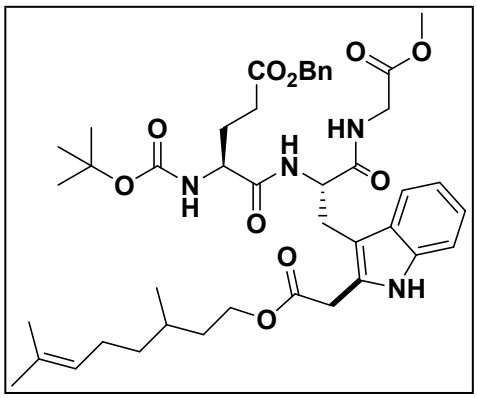
Hz, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 173.3, 172.7, 172.0, 171.8, 170.7, 169.9, 156.0, 135.8, 135.7, 130.3, 128.7, 128.7, 128.45 128.4, 122.0, 119.8, 118.2, 111.3, 107.4, 80.4, 66.7, 57.9, 54.5, 54.0, 52.3, 50.9, 41.4, 33.4, 31.0, 30.4, 28.3, 27.5, 26.8, 19.2, 19.1, 18.1. **HRMS (ESI):** m/z calc. for $C_{39}H_{51}N_5NaO_{11}$ $[M+Na]^+$ 788.3477, found 788.3480.

Methyl (6S,9S)-9-((2-(2-(4-allyl-2-methoxyphenoxy)-2-oxoethyl)-1H-indol-3-yl)methyl)-6-(3-(benzyloxy)-3-oxopropyl)-2,2-dimethyl-4,7,10-trioxo-3-oxa-5,8,11-triazatridecan-13-oate



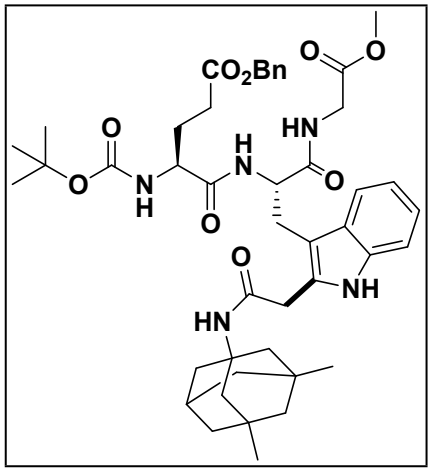
Compound **4v** was prepared according to general procedure **D**, Boc-Glu(OBn)-Trp-Gly-OMe (158 mg, 0.20 mmol) and 4-allyl-2-methoxyphenyl 2-bromoacetate (29 mg, 0.10 mmol). Flash column chromatography purification (CH_2Cl_2/ EtOAc 7:3) afforded compound **4v** (42 mg, 52%) as a pale brown amorphous solid . **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.80 (s, 1H), 7.53 (d, *J* = 7.6 Hz, 1H), 7.32 – 7.17 (m, 7H), 7.06 (dt, *J* = 18.3, 7.1 Hz, 2H), 6.96 (dd, *J* = 11.2, 7.9 Hz, 2H), 6.70 (d, *J* = 9.7 Hz, 2H), 6.51 (s, 1H), 5.93-5.81 (m, 1H), 5.24 – 5.19 (m, 1H), 5.01 – 5.05 (m, 3H), 5.00 (s, 1H), 4.71 (q, *J* = 6.7 Hz, 1H), 4.12 – 3.95 (m, 3H), 3.80 (dt, *J* = 16.6, 5.6 Hz, 1H), 3.72 (s, 3H), 3.63 (dd, *J* = 18.0, 5.4 Hz, 1H), 3.51 (s, 3H), 3.29 (m, 3H), 3.11 (dd, *J* = 14.6, 8.0 Hz, 1H), 2.29 (t, *J* = 7.1 Hz, 2H), 1.99 – 1.93 (m, 1H), 1.78 (m, 1H), 1.24 (s, 9H).**^{13}C NMR** (101 MHz, $CDCl_3$) δ 173.2, 171.4, 169.6, 169.3, 155.9, 150.6, 139.6, 137.8, 137.0, 135.9, 135.8, 128.7, 128.6, 128.4, 128.4, 128.2, 122.6, 122.4, 121.0, 120.1, 118.6, 116.4, 112.9, 111.07, 108.3, 80.4, 66.7, 56.0, 54.7, 53.7, 52.2, 41.4, 40.2, 31.9, 30.5, 28.3, 27.4, 26.9. **HRMS (ESI):** m/z calc. for $C_{43}H_{50}N_4NaO_{11}$ $[M+Na]^+$ 821.3368 found 821.3380.

Methyl (6S,9S)-6-(3-(benzyloxy)-3-oxopropyl)-9-((2-(2-((3,7-dimethyloct-6-en-1-yl)oxy)-2-oxoethyl)-1H-indol-3-yl)methyl)-2,2-dimethyl-4,7,10-trioxo-3-oxa-5,8,11-triazatridecan-13-oate



Compound **4x** was prepared according to general procedure **D**, Boc-Glu(OBn)-Trp-Gly-OMe (158 mg, 0.20 mmol) and 3,7-dimethyloct-6-en-1-yl carbonobromidate (26 mg, 0.10 mmol). Flash column chromatography purification (CH_2Cl_2/ EtOAc 8:2) afforded compound **4x** (48 mg, 55%) as a pale brown amorphous solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.49 (s, 1H), 7.49 (d, *J* = 7.6 Hz, 1H), 7.24 –7.31 (m, 5H), 7.20 (d, *J*= 6.5 Hz, 1H), 7.12 – 6.97 (m, 4H), 6.64 (t, *J* = 6.3 Hz, 1H), 5.25 (d, *J* = 6.8 Hz, 1H), 5.04 (s, 2H), 5.01 (d, *J* = 8.8 Hz, 1H), 4.70 (q, *J* = 6.5 Hz, 1H), 4.07-4.17 (m, 2H), 3.99 (q, *J* = 6.8 Hz, 1H), 3.80 – 3.87 (m, 1H), 3.83 – 3.68 (m, 2H), 3.62 (dd, *J* = 18.0, 5.3 Hz, 1H), 3.55 (s, 3H), 3.27 – 3.06 (m, 2H), 2.26 (t, *J* = 7.1 Hz, 2H), 1.92 (m, 4H), 1.78 (m, 2H), 1.61 (s, 3H), 1.53 (s, 3H), 1.50 – 1.34 (m, 2H), 1.25 (s, 9H), 1.19 – 1.06 (m, 2H), 0.85 (d, *J* = 6.5 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 173.3, 171.6, 171.5, 169.7, 155.9, 135.8, 135.7, 131.6, 129.0, 128.7, 128.5, 128.4, 128.0, 124.6, 122.4, 120.1, 118.5, 111.1, 108.2, 80.4, 66.7, 64.5, 54.7, 53.5, 52.3, 41.3, 37.1, 35.5, 31.8, 30.4, 29.6, 28.3, 27.4, 26.6, 25.9, 25.5, 19.5, 17.8. **HRMS (ESI):** m/z calc. for $C_{43}H_{59}N_4O_{10}$ $[M+H]^+$ 791.4226 found 791.4230.

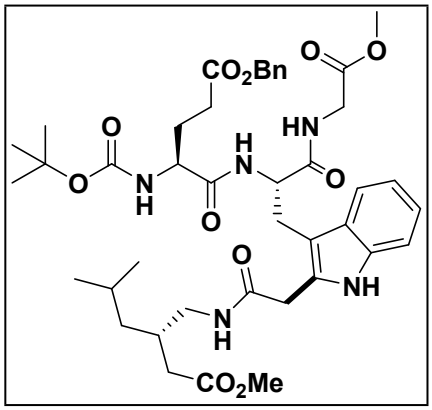
Methyl (6S,9S)-6-(3-(benzyloxy)-3-oxopropyl)-9-((2-(2-((3,5-dimethyladamantan-1-yl)amino)-2-oxoethyl)-1H-indol-3-yl)methyl)-2,2-dimethyl-4,7,10-trioxo-3-oxa-5,8,11-triazatridecan-13-oate



Compound **4y** was prepared according to general procedure **D**, Boc-Glu(OBn)-Trp-Gly-OMe (158 mg, 0.20 mmol) and 2-bromo-*N*-(3,5-dimethyladamantan-1-yl)acetamide (30 mg, 0.10 mmol). Flash column chromatography purification (CH_2Cl_2/ EtOAc 8:2) afforded compound **4y** (53 mg, 65%) as an pale brown amorphous solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.21 (s, 1H), 7.54 – 7.47 (m, 1H), 7.41 (d, *J* = 7.7 Hz, 1H), 7.30 – 7.22 (m, 4H), 7.20 (dd, *J* = 3.8, 3.0 Hz, 1H), 7.02 (t, *J* = 7.5 Hz, 2H), 6.98 (d, *J* = 7.6 Hz, 1H), 6.75 (s, 1H), 6.52 (s, 1H), 5.39 (d, *J* = 7.1 Hz, 1H), 5.02 (s, 2H), 4.66 (q, *J* = 7.0 Hz, 1H), 4.04 (q, *J* = 7.0 Hz, 1H), 3.81 (dd, *J* = 17.9, 5.7 Hz, 1H), 3.64 (dd, *J* = 18.0, 5.7 Hz, 1H), 3.56 – 3.52 (m, 5H), 3.21 – 3.06 (m, 2H), 2.31 (t, *J* = 7.4 Hz, 2H), 2.05 (m, 1H), 1.97 (m, 1H), 1.79 – 1.69 (m, 3H), 1.63 – 1.49 (m, 4H), 1.25 (s, 9H), 1.23 – 1.15 (m, 4H), 1.12 – 0.99 (m, 2H), 0.77 (s, 3H), 0.75 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 173.1, 172.1, 171.8, 169.6, 169.5, 155.9, 135.6, 131.2, 128.6, 128.3, 128.3, 128.0, 121.8, 121.1, 119.5, 118.0, 111.2, 106.7, 80.3, 66.6, 54.5, 54.0, 53.5, 52.2, 50.6, 50.5, 47.6, 47.4, 47.3, 42.6, 41.3,

40.1, 39.8, 34.5, 32.3, 30.4, 30.1, 28.2, 27.3, 26.5, 24.7. **HRMS (ESI):** m/z calc. for $C_{45}H_{60}N_5O_9$ $[M+H]^+$ 814.4386, found 814.4389.

Methyl (6S,9S)-6-(3-(benzyloxy)-3-oxopropyl)-9-((2-(2-(((S)-2-(2-methoxy-2-oxoethyl)-4-methylpentyl)amino)-2-oxoethyl)-1H-indol-3-yl)methyl)-2,2-dimethyl-4,7,10-trioxo-3-oxa-5,8,11-triazatridecan-13-oate



Compound **4z** was prepared according to general procedure procedure **D**, Boc-Glu(OBn)-Trp-Gly-OMe (158 mg, 0.20 mmol) and methyl (*S*)-3-((2-bromoacetamido)methyl)-5-methylhexanoate (29 mg, 0.10 mmol). Preparative HPLC isolation (H_2O:MeCN 30:70) afforded compound **4z** (41 mg, 51%) as a pale brown amorphous solid. . **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.13 (s, 1H), 7.47 (d, *J* = 7.6 Hz, 1H), 7.43 (d, *J* = 7.8 Hz, 1H), 7.37 – 7.31 (m, 5H), 7.26 (d, *J*= 6.7 HZ, 1H), 7.09 (t, *J* = 7.3 Hz, 1H), 7.04 (t, *J* = 7.1 Hz, 2H), 5.37 (d, *J* = 7.3 Hz, 1H), 5.10 (s, 2H), 4.73 (q, *J* = 7.0 Hz, 1H), 4.11 (q, *J* = 7.0 Hz, 1H), 3.92 (dd, *J* = 17.9, 5.7 Hz, 1H), 3.72 (m, 2H), 3.66 (s, 1H), 3.61 (s, 3H), 3.55 (s, 3H), 3.47 (s, 1H), 3.34 – 3.07 (m, 4H), 2.35 (m, 2H), 2.28 (dd, *J* = 10.5, 6.4 Hz, 2H), 1.95-2.06 (m, 1H), 2.06 – 1.95 (m, 1H), 1.88 – 1.76 (m, 1H), 1.66 – 1.54 (m, 1H), 1.35 (s, 9H), 1.13 (m, 2H), 0.85(d, *J* = 6.5 Hz, 3H), 0.83 (d, *J* = 6.6 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 174.1, 173.2, 171.9, 171.8, 170.7, 169.7, 155.9, 135.8, 135.8, 130.6, 128.7, 128.5, 128.4, 128.2, 122.0, 119.7, 118.2, 111.2, 107.5, 80.4, 77.4, 66.7, 54.5, 52.3, 51.8, 43.8, 42.0, 41.4, 37.7, 33.9, 33.4, 30.5, 28.3, 27.4, 27.3, 25.3, 22.8, 22.7; **HRMS (ESI):** m/z calc. for $C_{42}H_{58}N_5O_{11}$ $[M+H]^+$ 808.4127 found 808.4133.

8. Spectra data

8.1. Starting materials

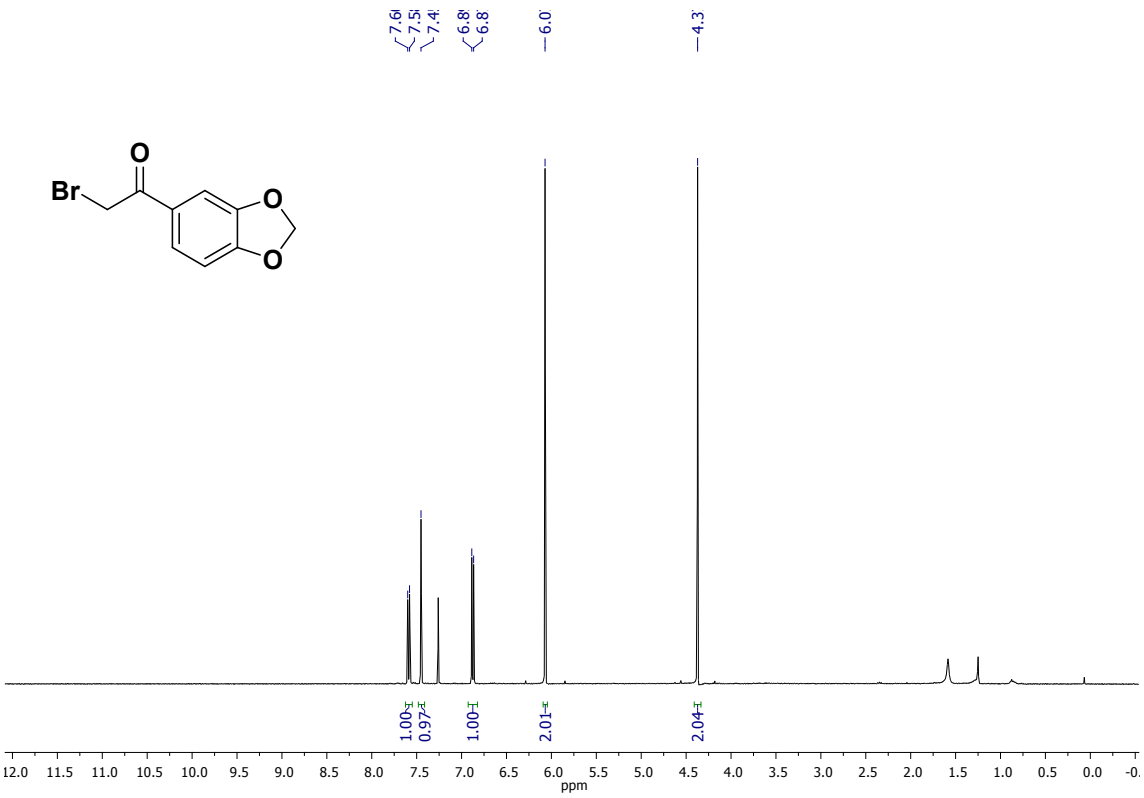


Figure S1. ^{1}H NMR (400 MHz, $CDCl_3$) of **2c**

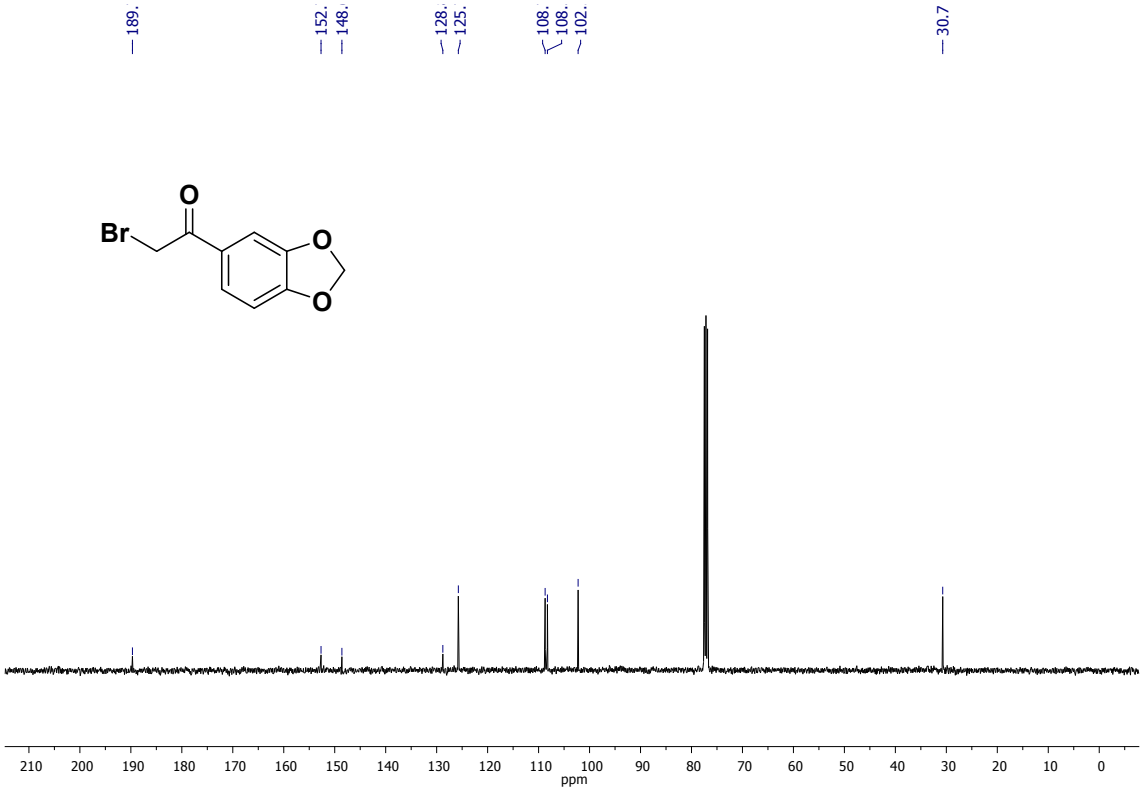


Figure S2. ^{13}C NMR (101 MHz, $CDCl_3$) of **2c**

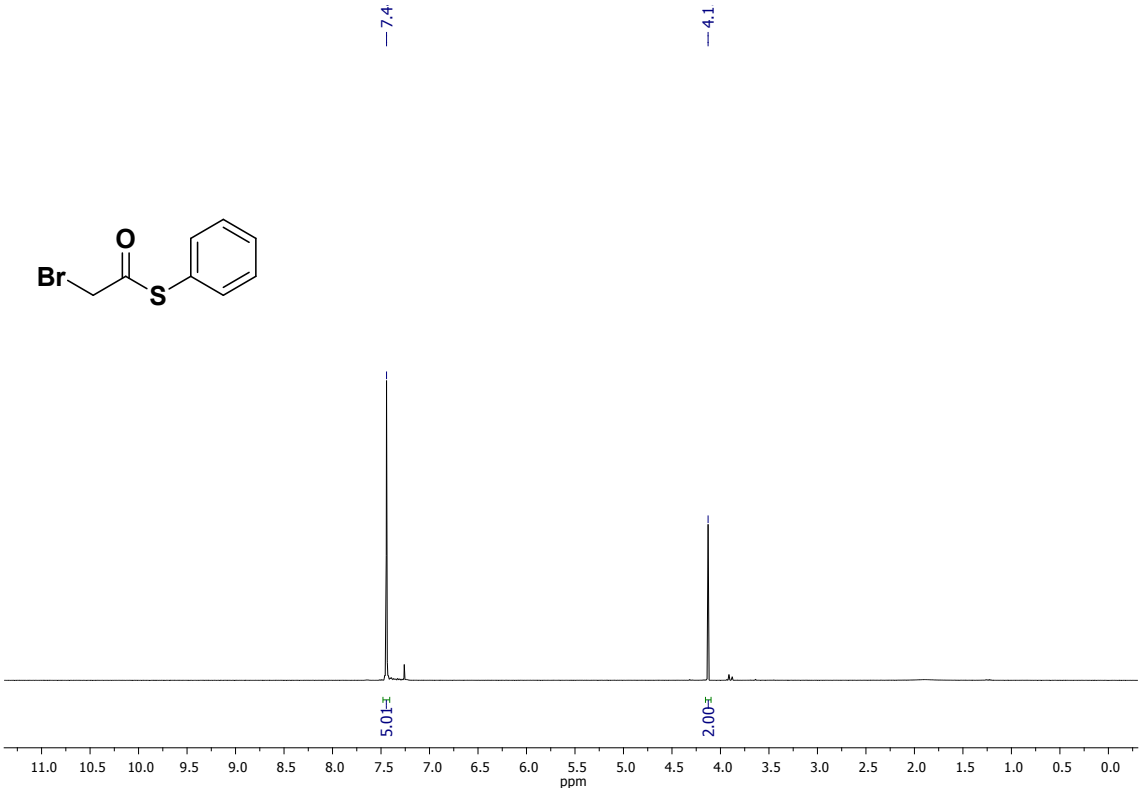


Figure S3. ^{1}H NMR (400 MHz, $CDCl_3$) of **2d**

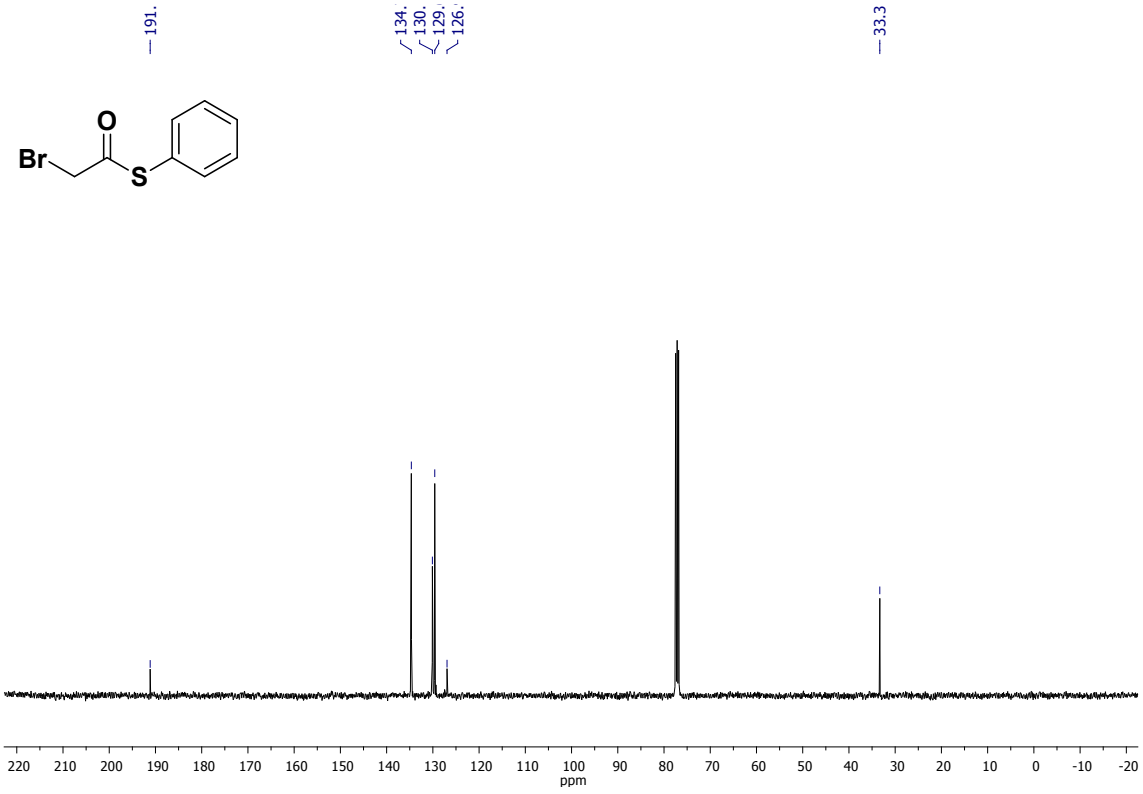


Figure S4. ^{13}C NMR (101 MHz, $CDCl_3$) of **2d**

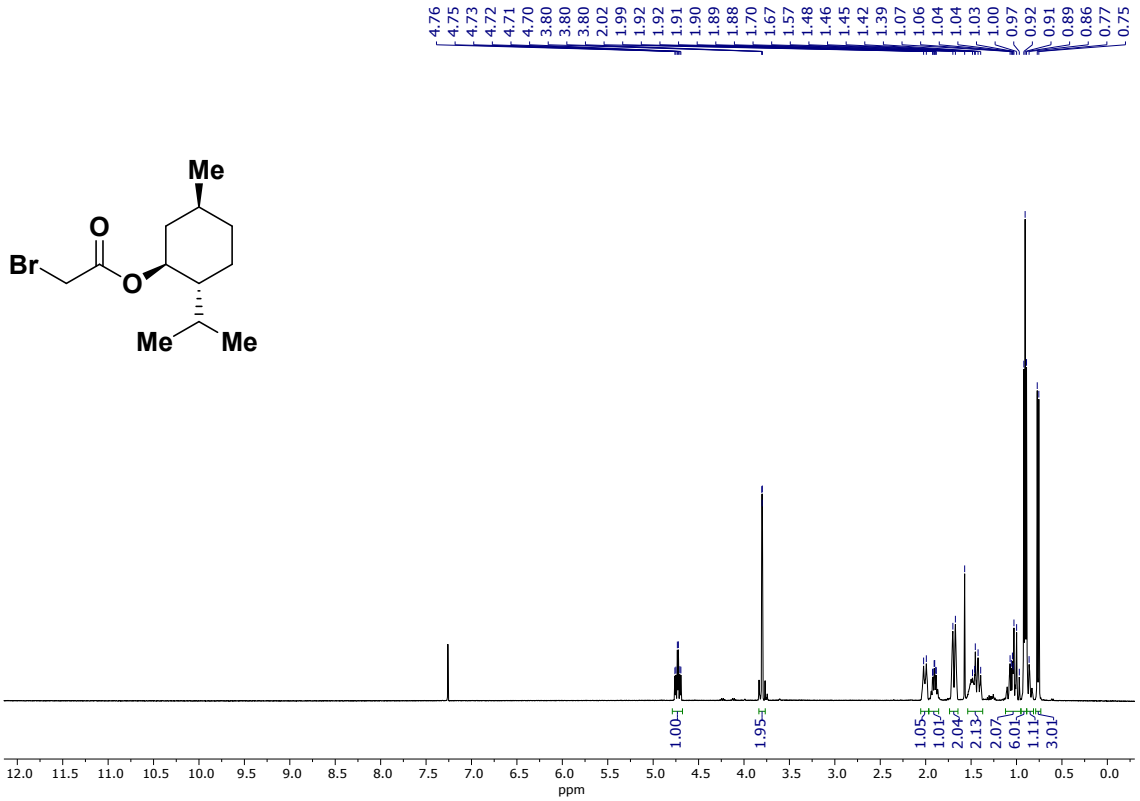


Figure S5. ^{1}H NMR (400 MHz, $CDCl_3$) of **2e**

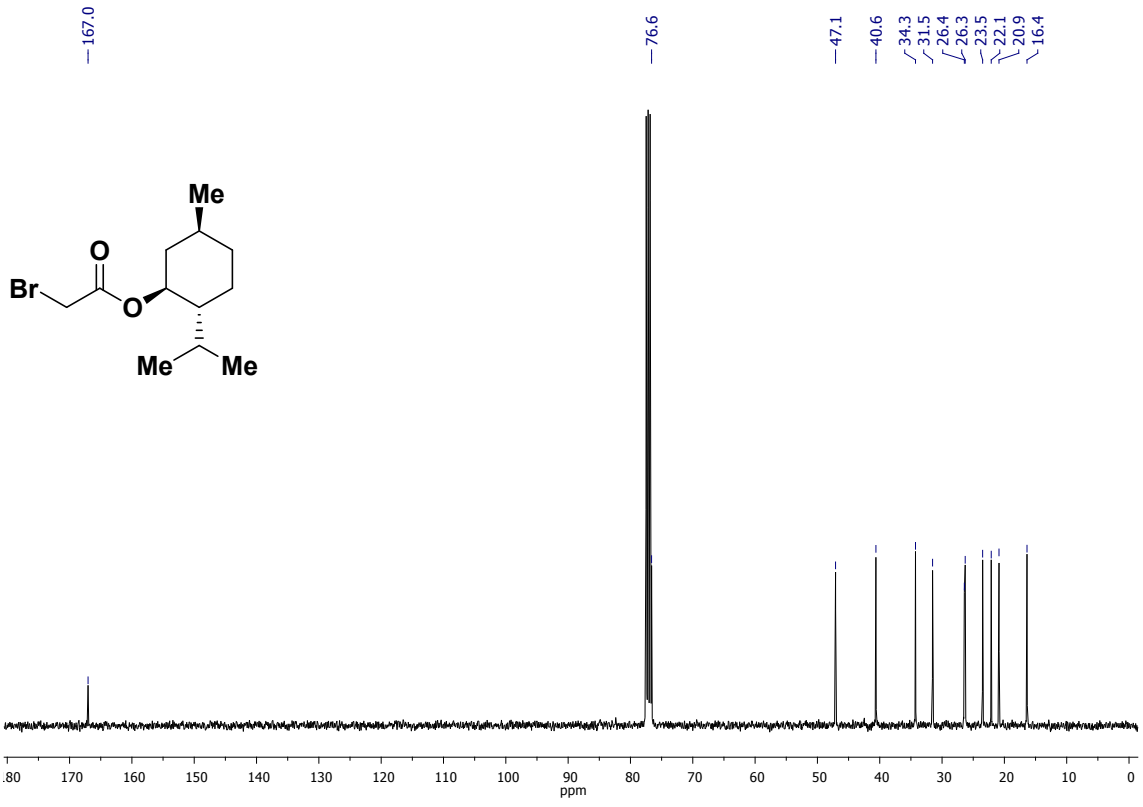


Figure S6. ^{13}C NMR (101 MHz, $CDCl_3$) of **2e**

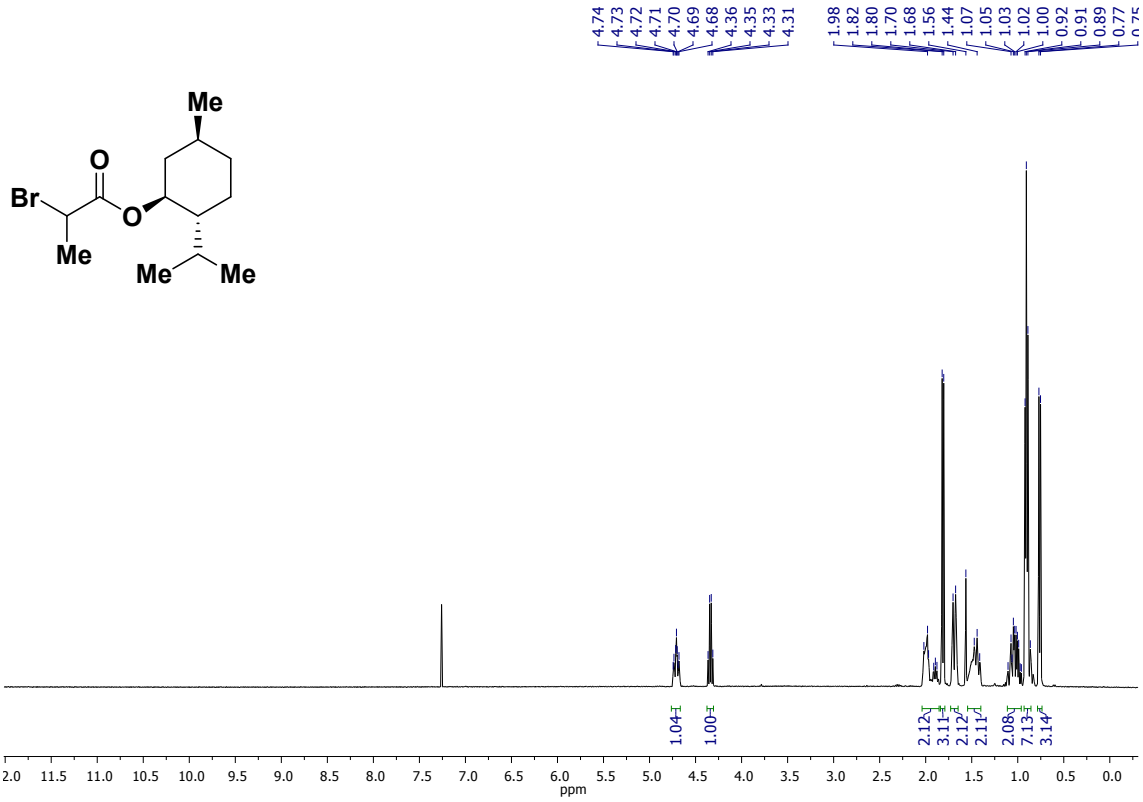


Figure S7. ^{1}H NMR (400 MHz, $CDCl_3$) of **2f**

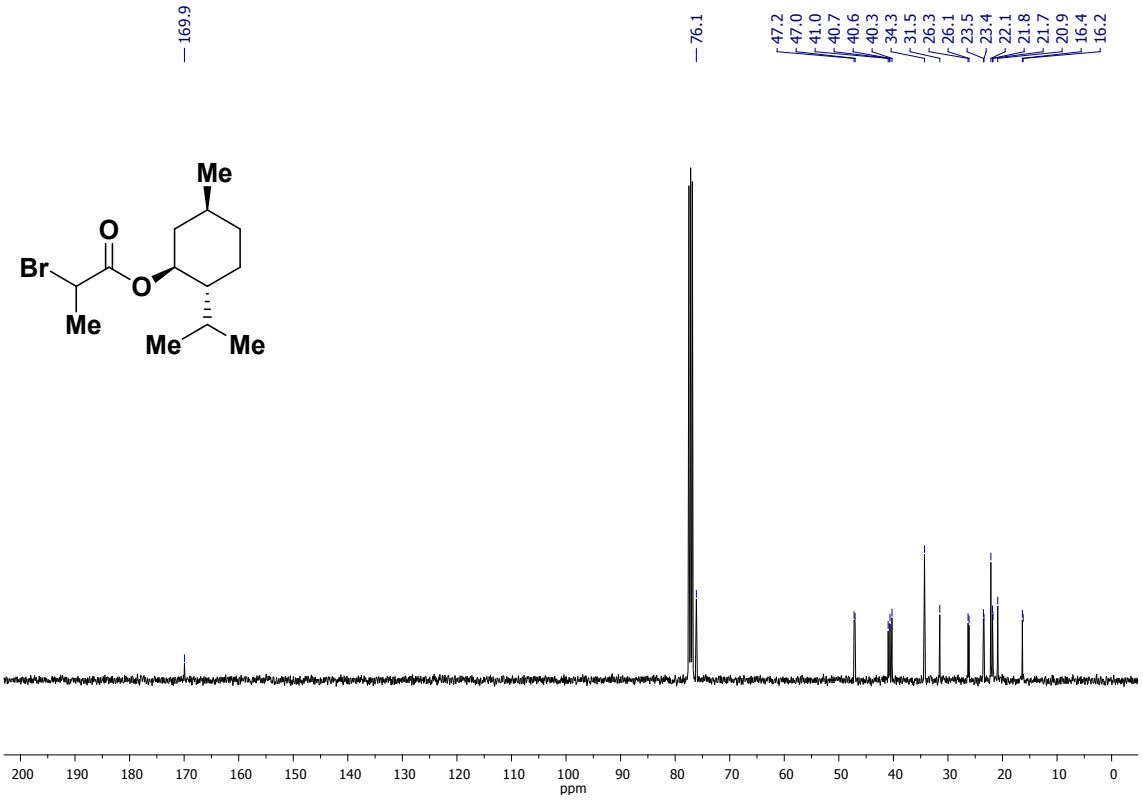


Figure S8. ^{13}C NMR (101 MHz, $CDCl_3$) of **2f**

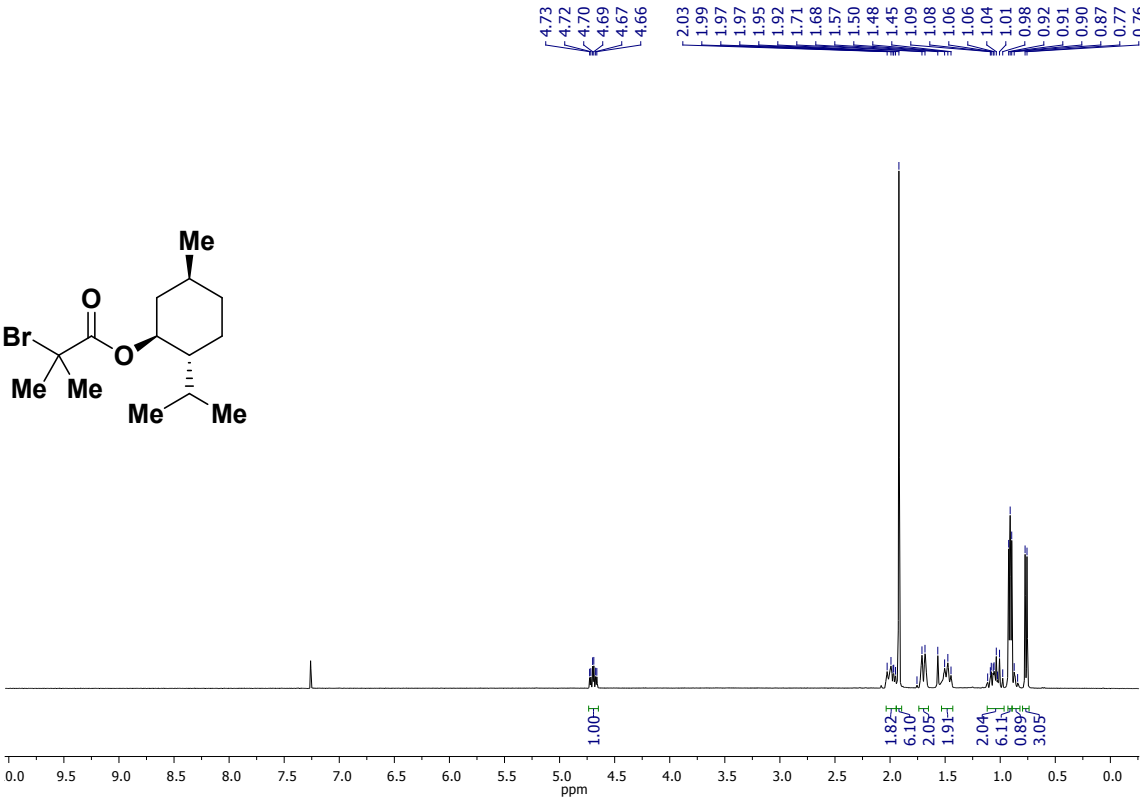


Figure S9. ^{1}H NMR (400 MHz, $CDCl_3$) of **2g**

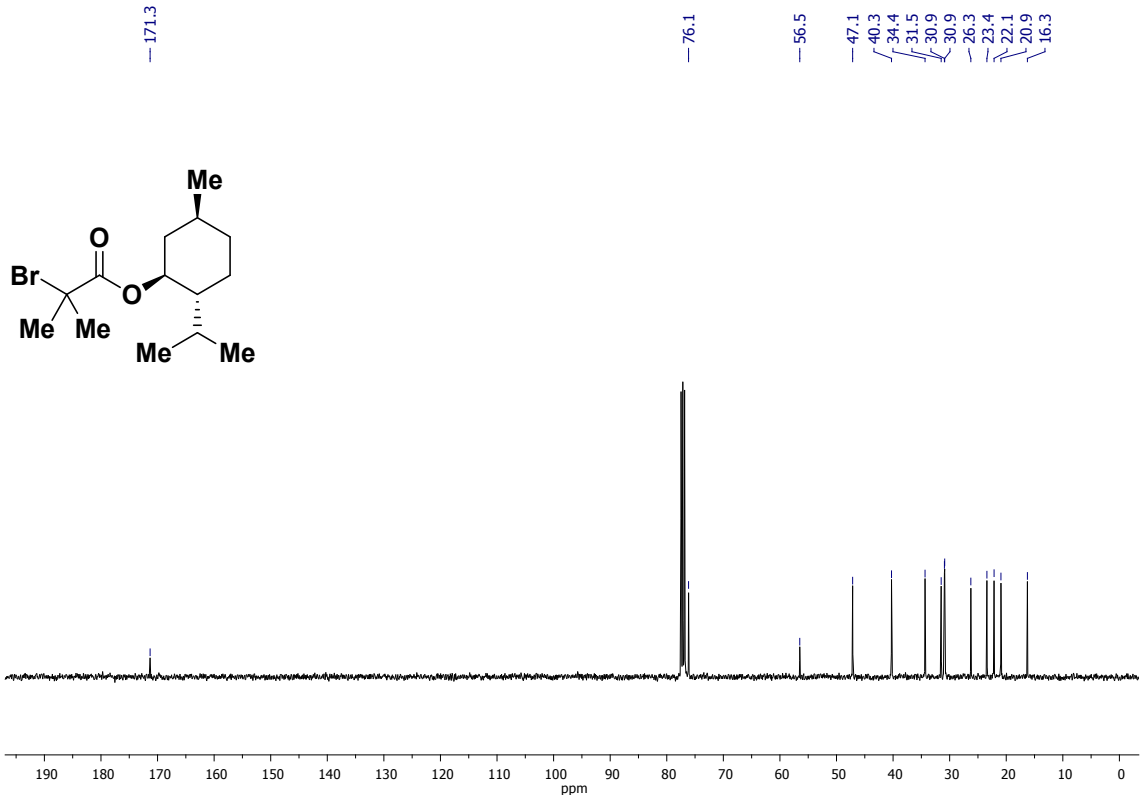


Figure S10. ^{13}C NMR (101 MHz, $CDCl_3$) of **2g**

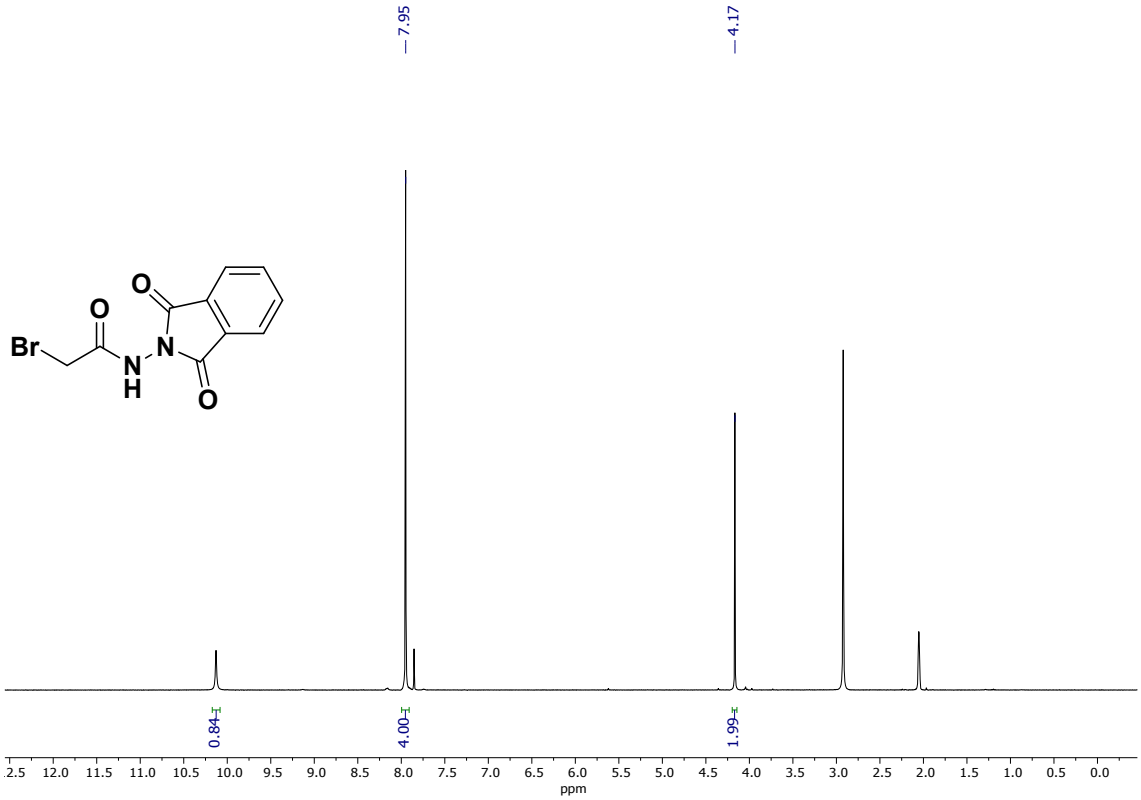


Figure S11. ^{1}H NMR (400 MHz, Acetone-d_6) of **2 h**

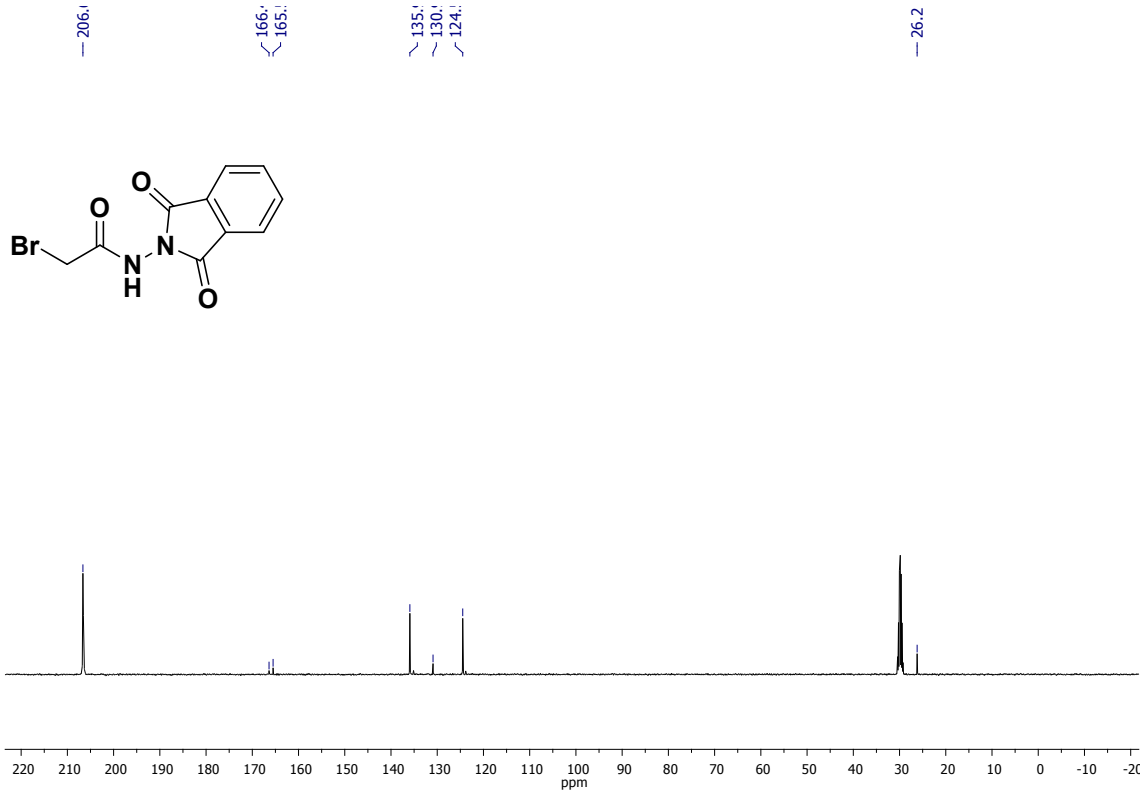


Figure S12. ^{13}C NMR (101 MHz, Acetone-d_6) of **2h**

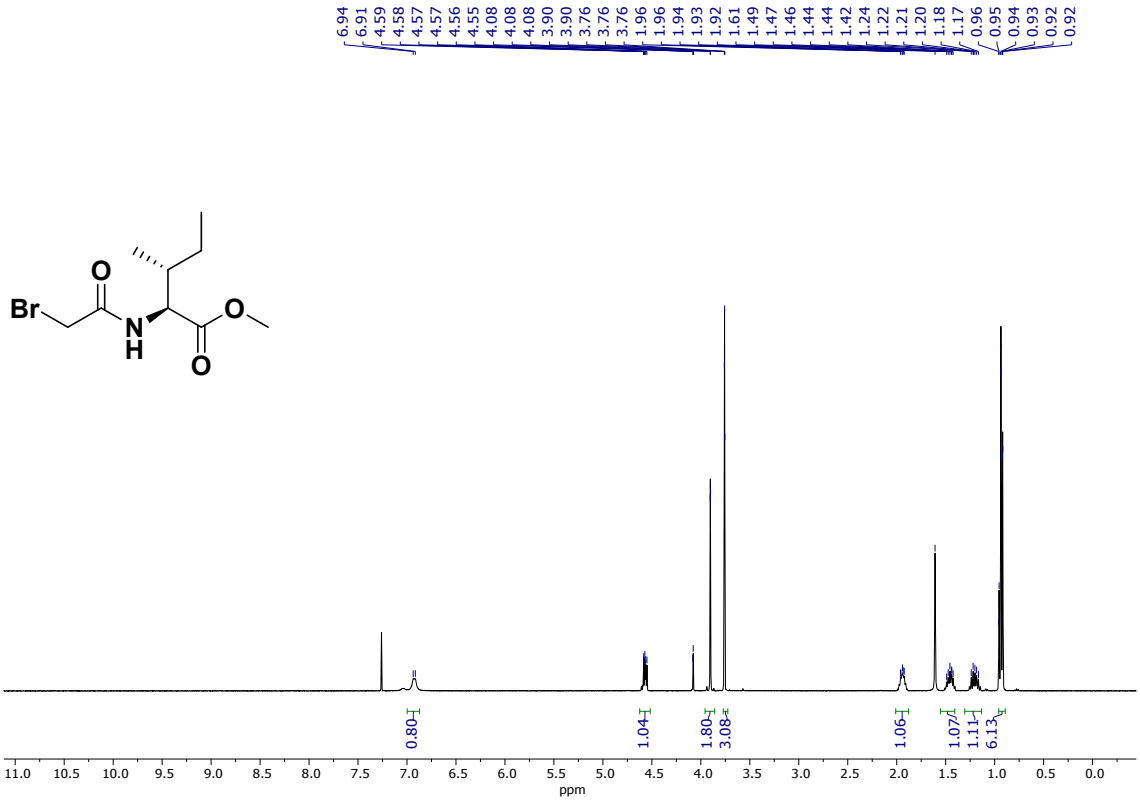


Figure S13. ^{1}H NMR (400 MHz, $CDCl_3$) of **2i**

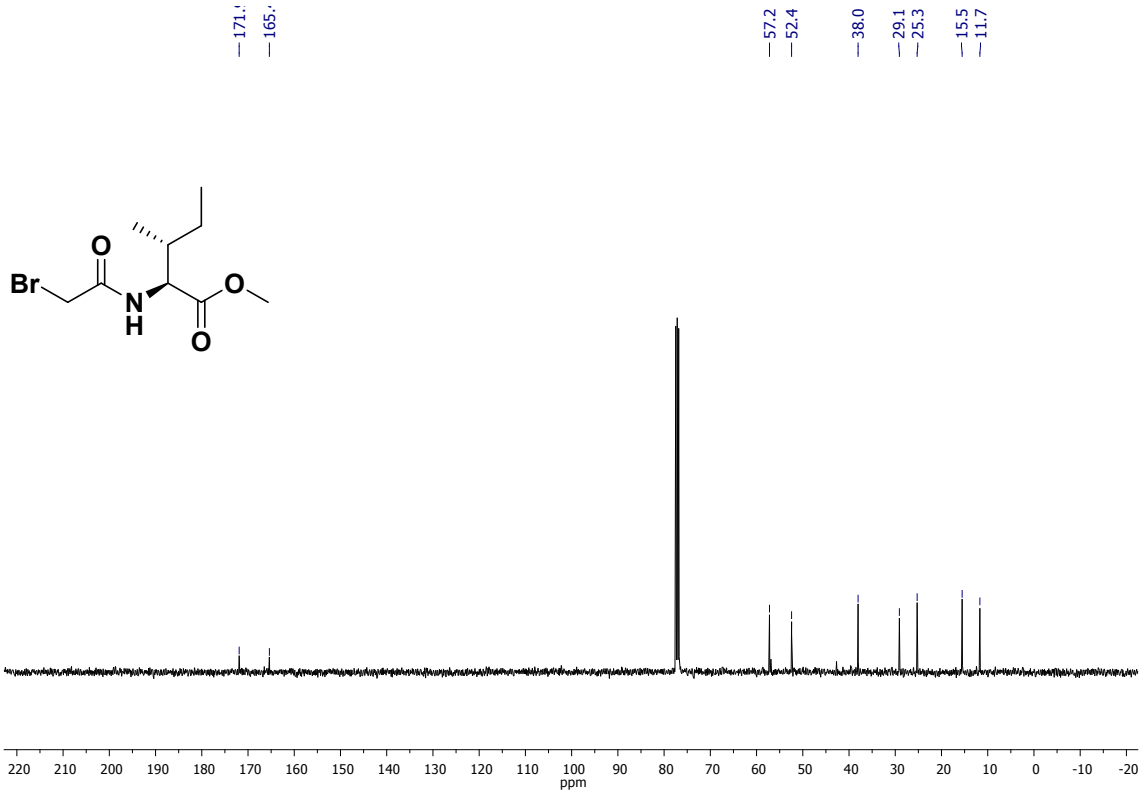


Figure S14. ^{13}C NMR (101 MHz, $CDCl_3$) of **2i**

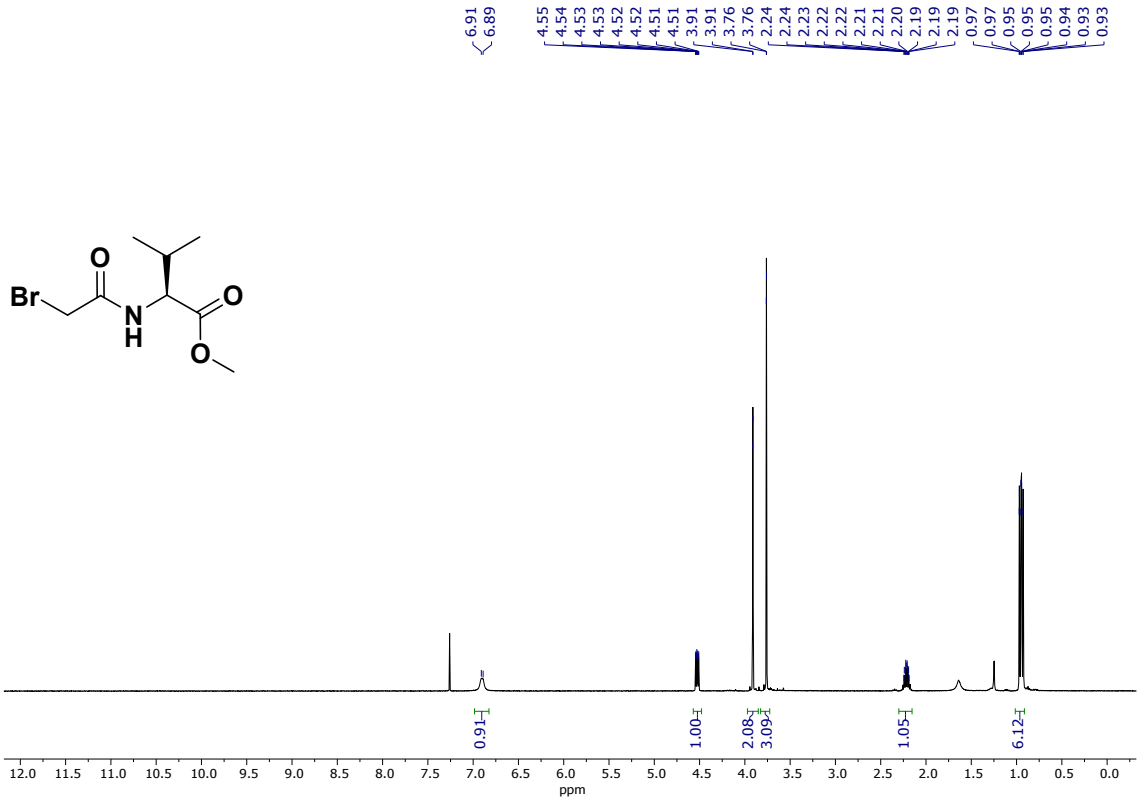


Figure S15. ^{1}H NMR (400 MHz, $CDCl_3$) of **2j**

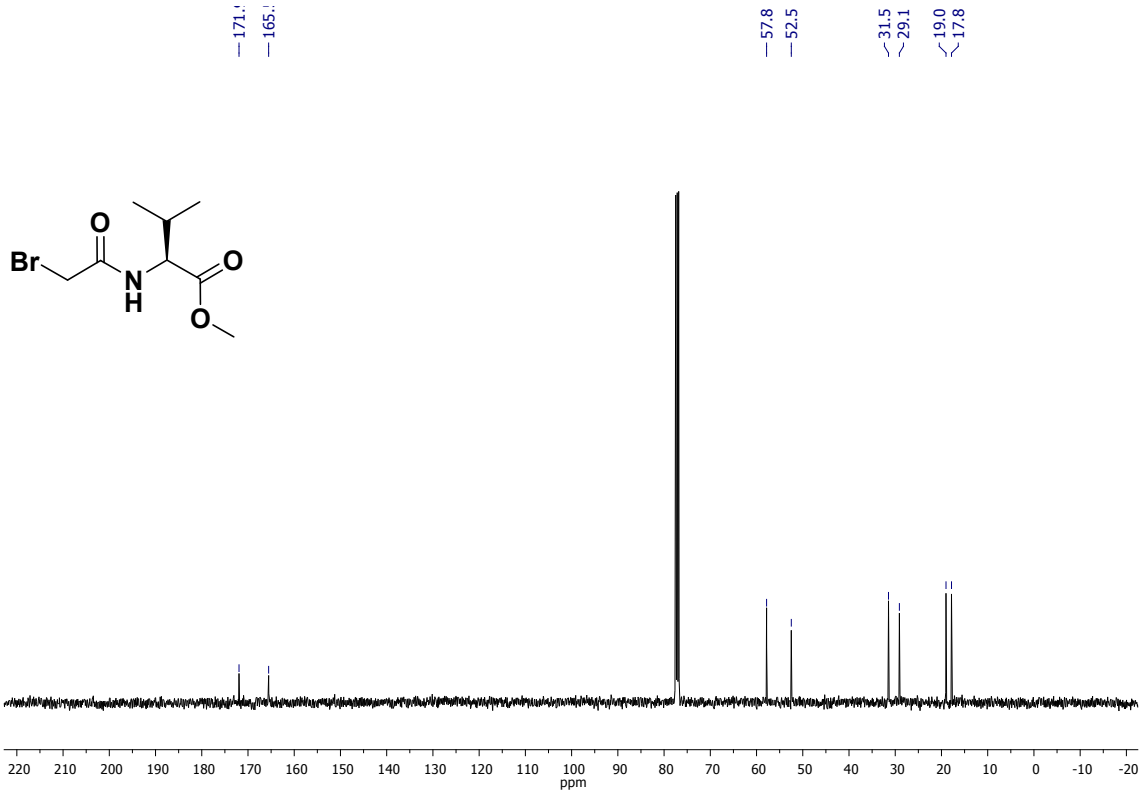


Figure S16. ^{13}C NMR (101 MHz, $CDCl_3$) of **2j**

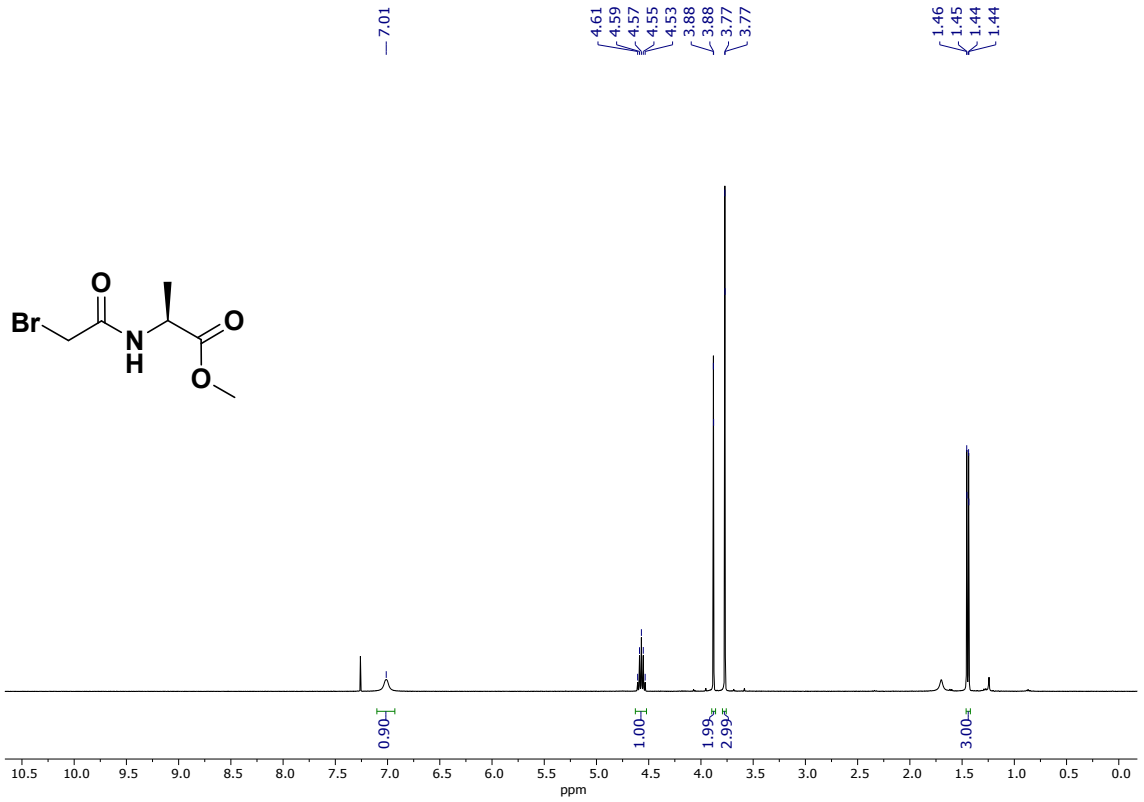


Figure S17. ^{1}H NMR (400 MHz, $CDCl_3$) of **2k**

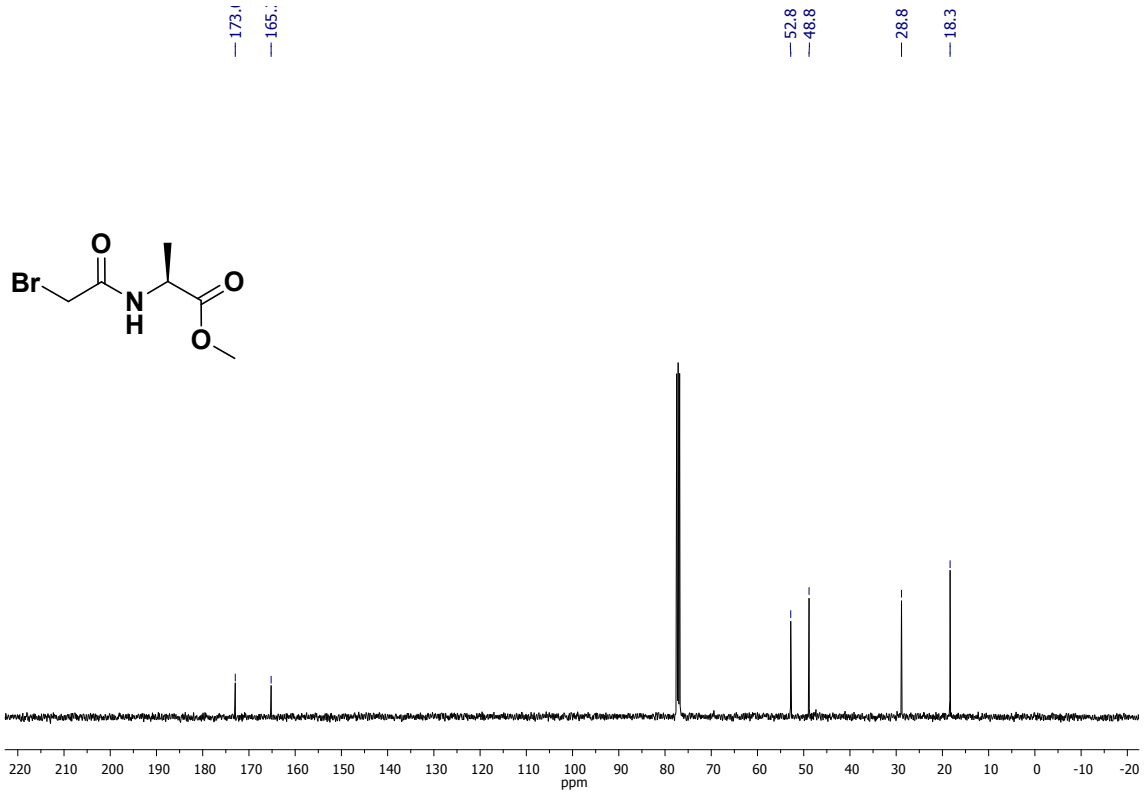


Figure S18. ^{13}C NMR (101 MHz, $CDCl_3$) of **2k**

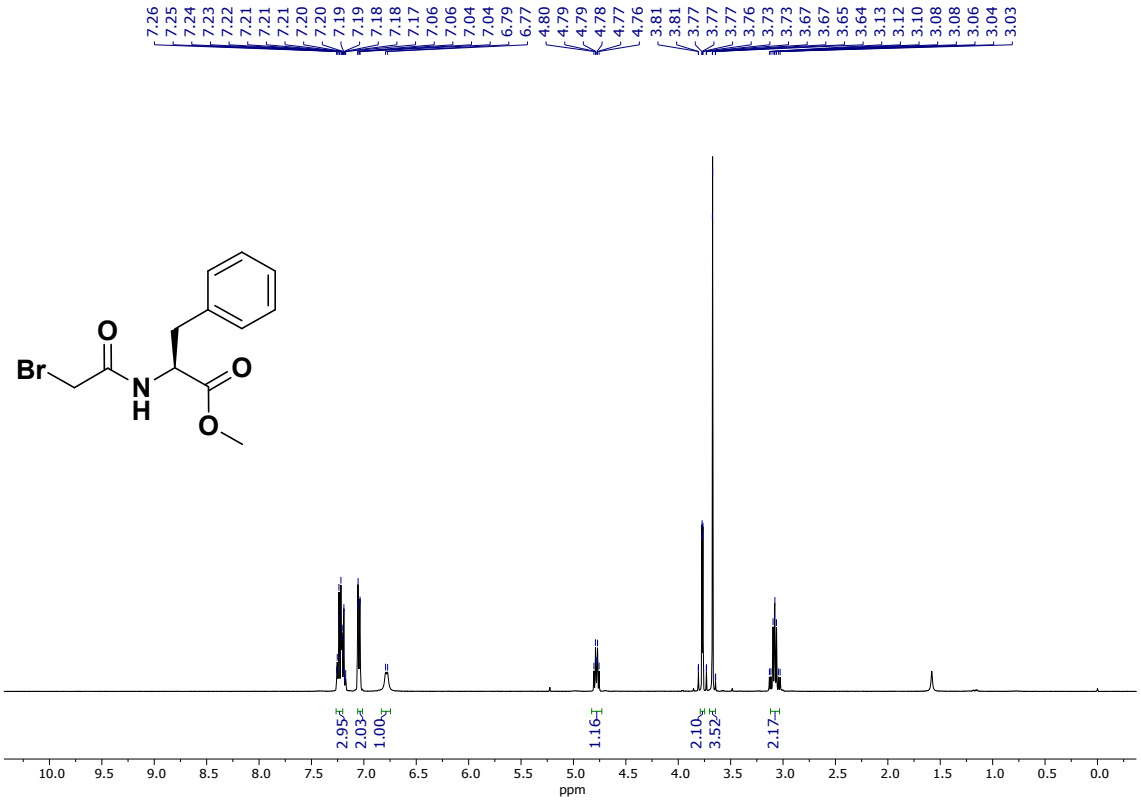


Figure S19. ^{1}H NMR (400 MHz, $CDCl_3$) of **2l**

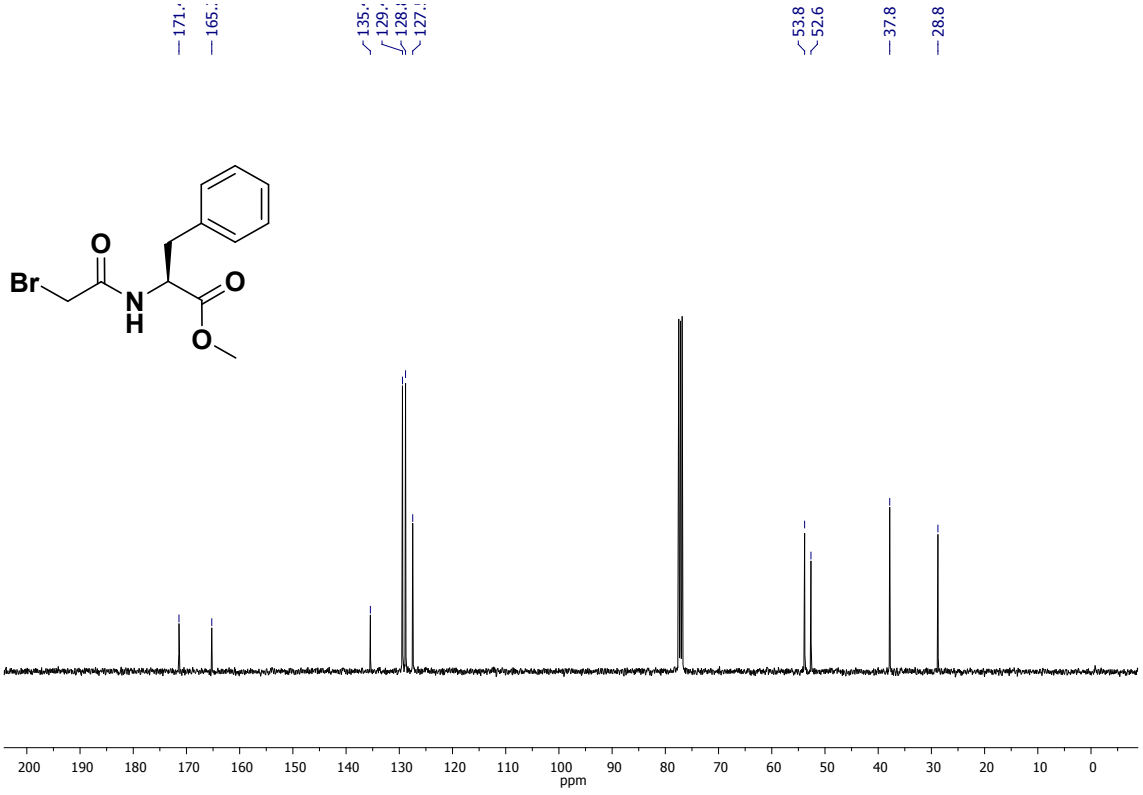


Figure S20.^{13}C NMR (101 MHz, $CDCl_3$) of **2l**

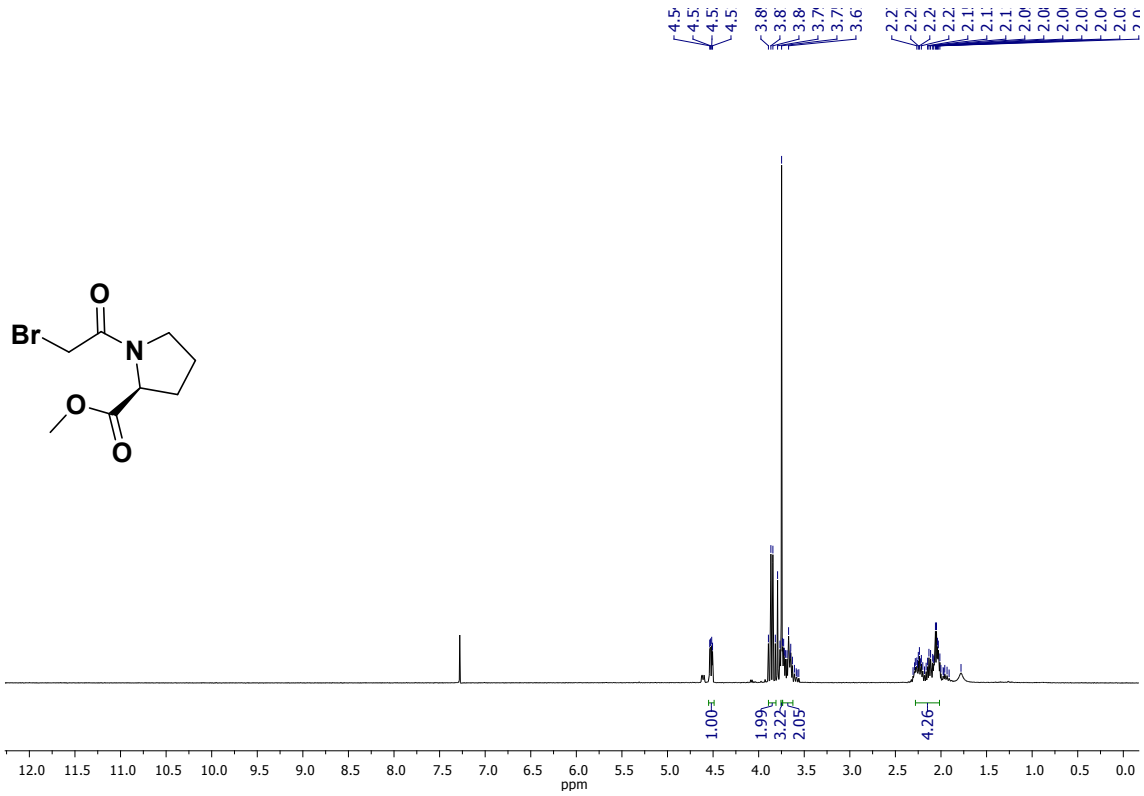


Figure S21. ^{1}H NMR (400 MHz, $CDCl_3$) of **2m**

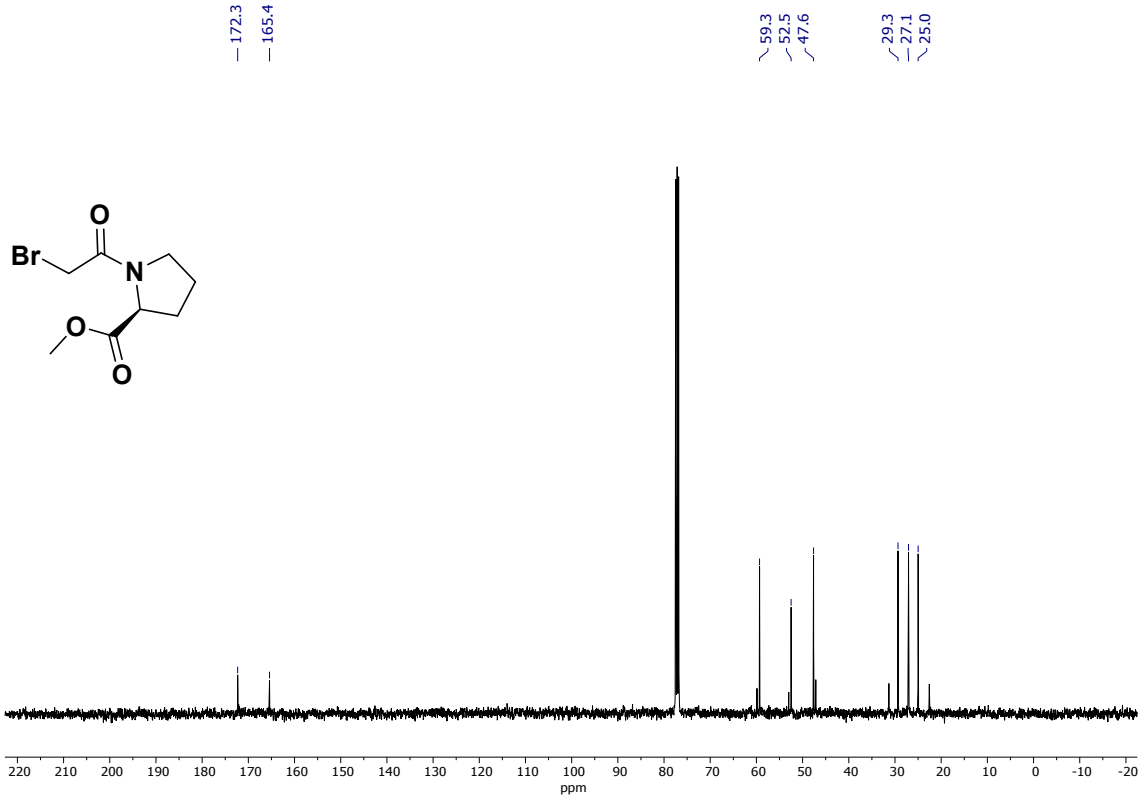


Figure S22. ^{13}C NMR (101 MHz, $CDCl_3$) of **2m**

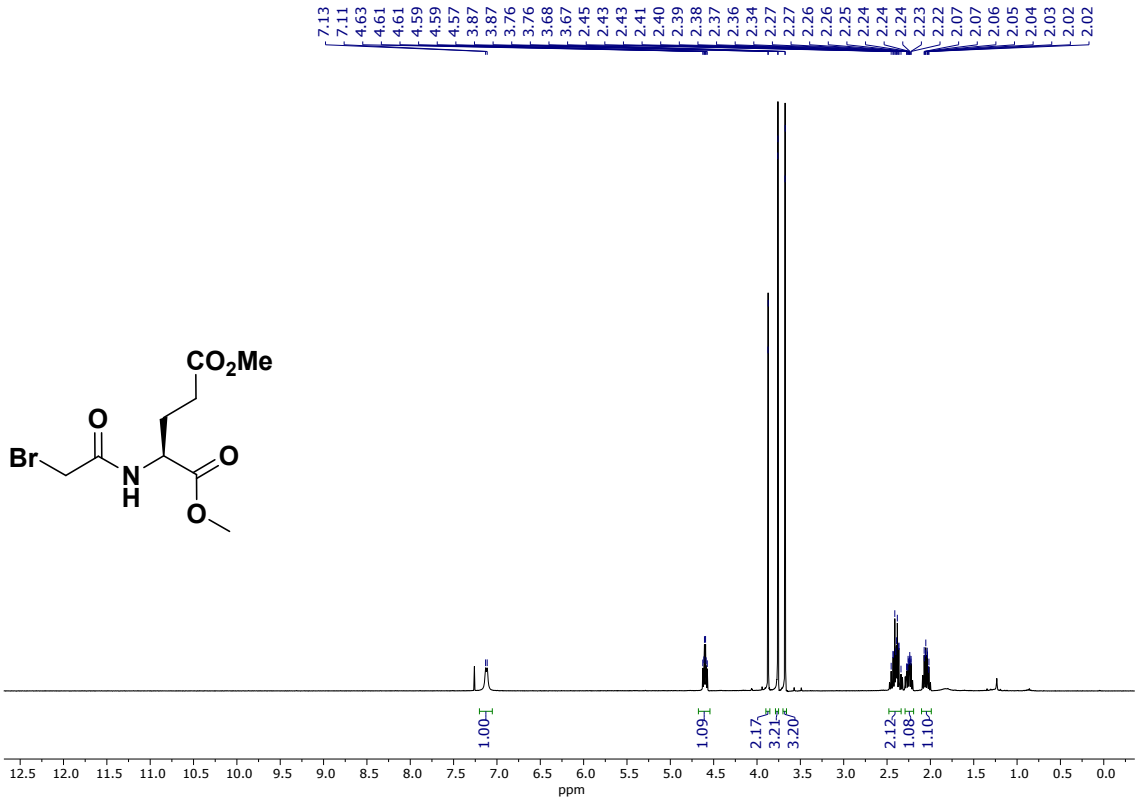


Figure S23. ^{1}H NMR (400 MHz, $CDCl_3$) of **2n**

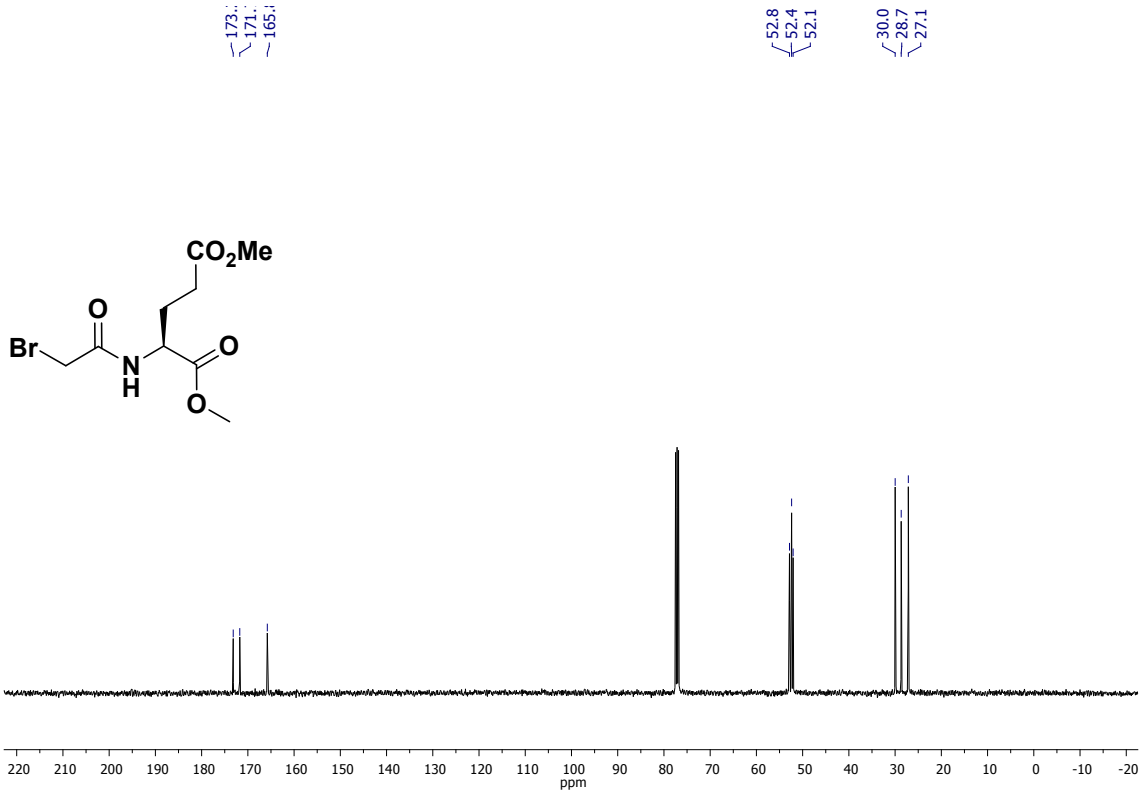


Figure S24. ^{13}C NMR (101 MHz, $CDCl_3$) of **2n**

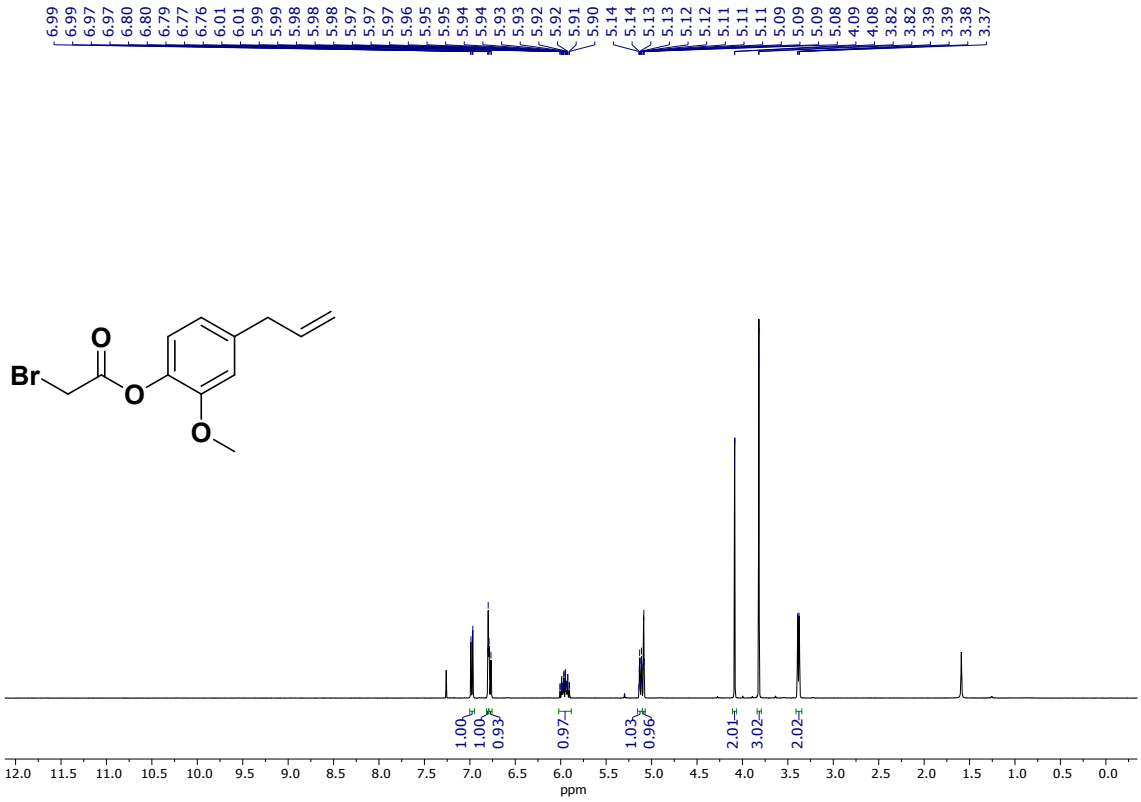


Figure S25. ^{1}H NMR (400 MHz, $CDCl_3$) of **2u**

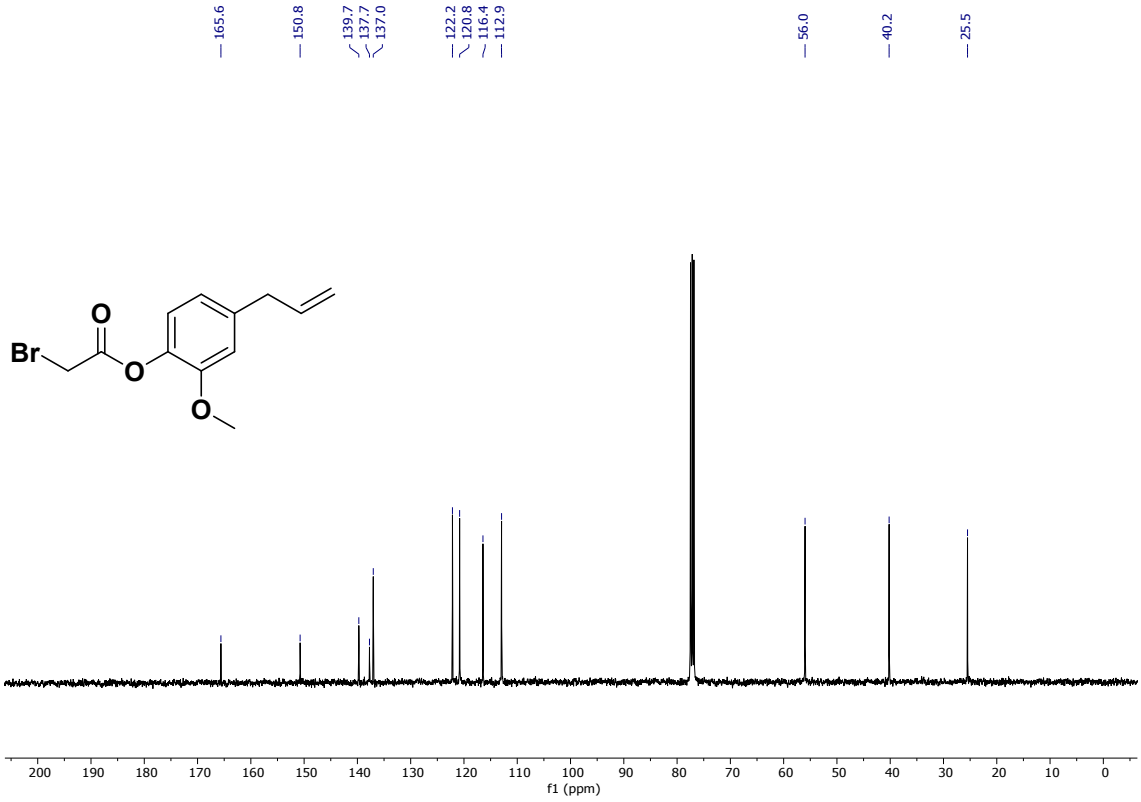


Figure S26. ^{13}C NMR (101 MHz, $CDCl_3$) of **2u**

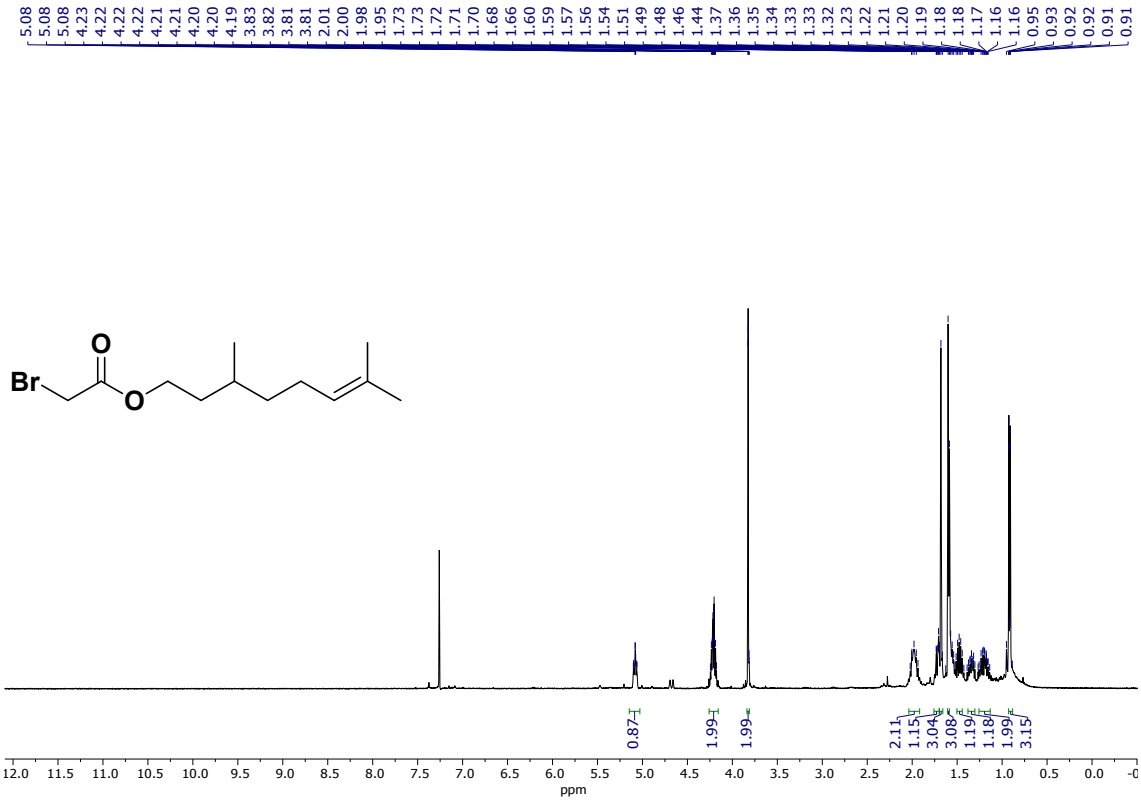


Figure S27. ^{1}H NMR (400 MHz, $CDCl_3$) of **2v**

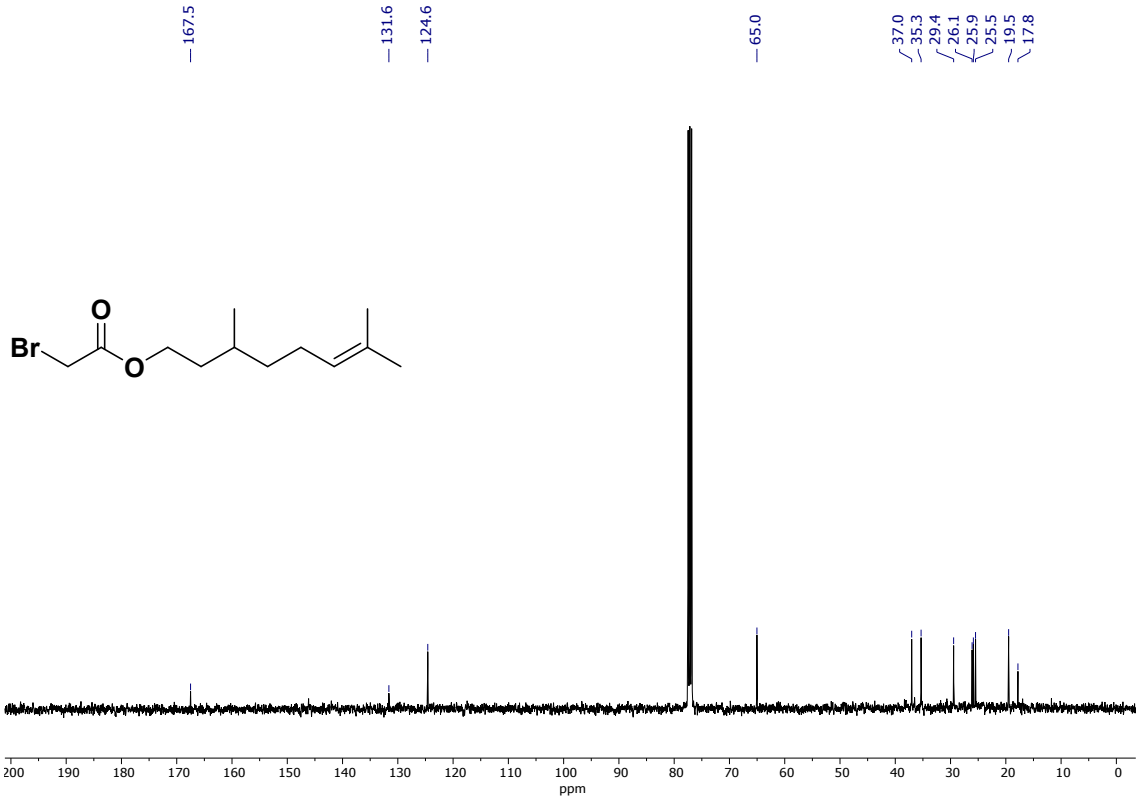


Figure S28. ^{13}C NMR (101 MHz, $CDCl_3$) of **2v**

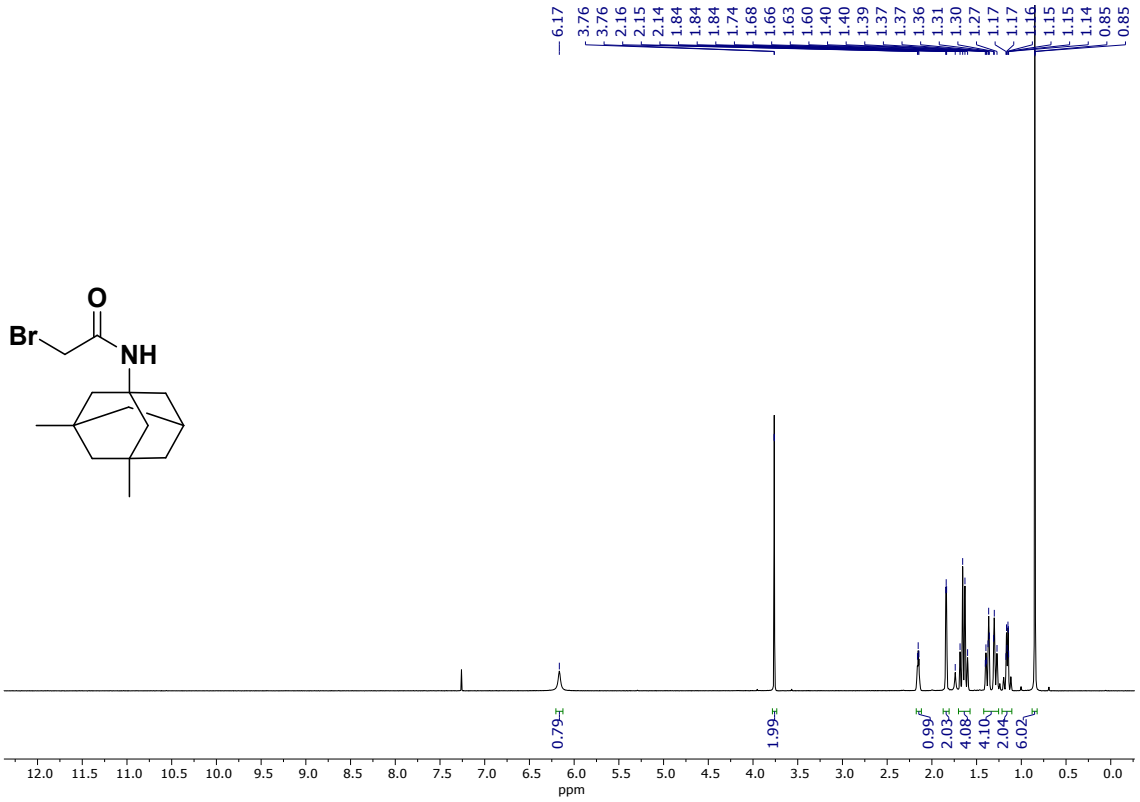


Figure S29. ^{1}H NMR (400 MHz, $CDCl_3$) of **2x**

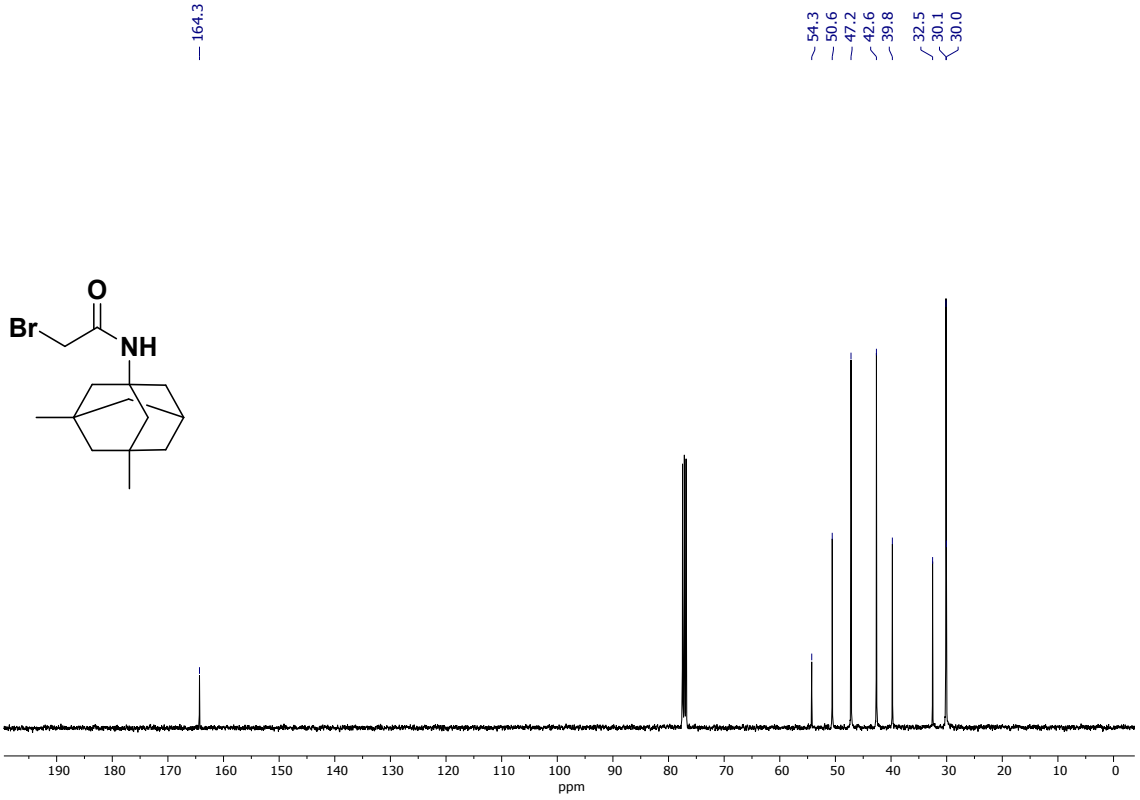


Figure S30. ^{13}C NMR (101 MHz, $CDCl_3$) of **2x**

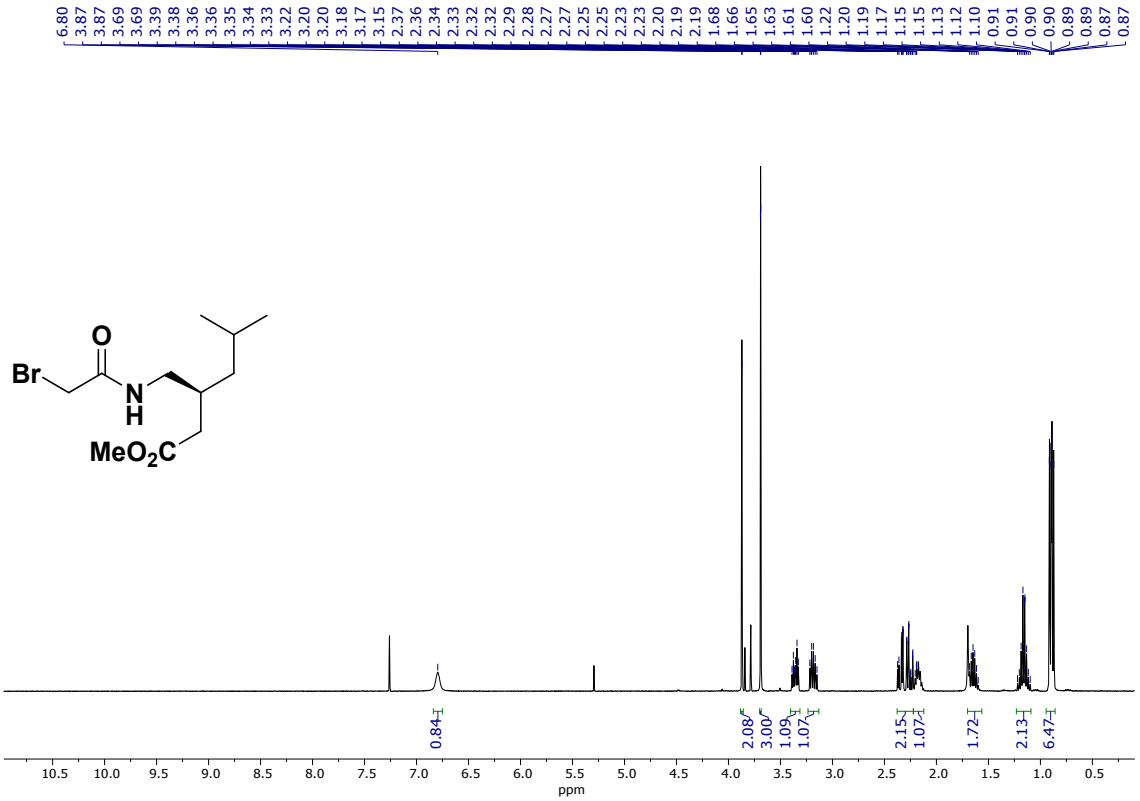


Figure S31. ^{1}H NMR (400 MHz, $CDCl_3$) of **2z**

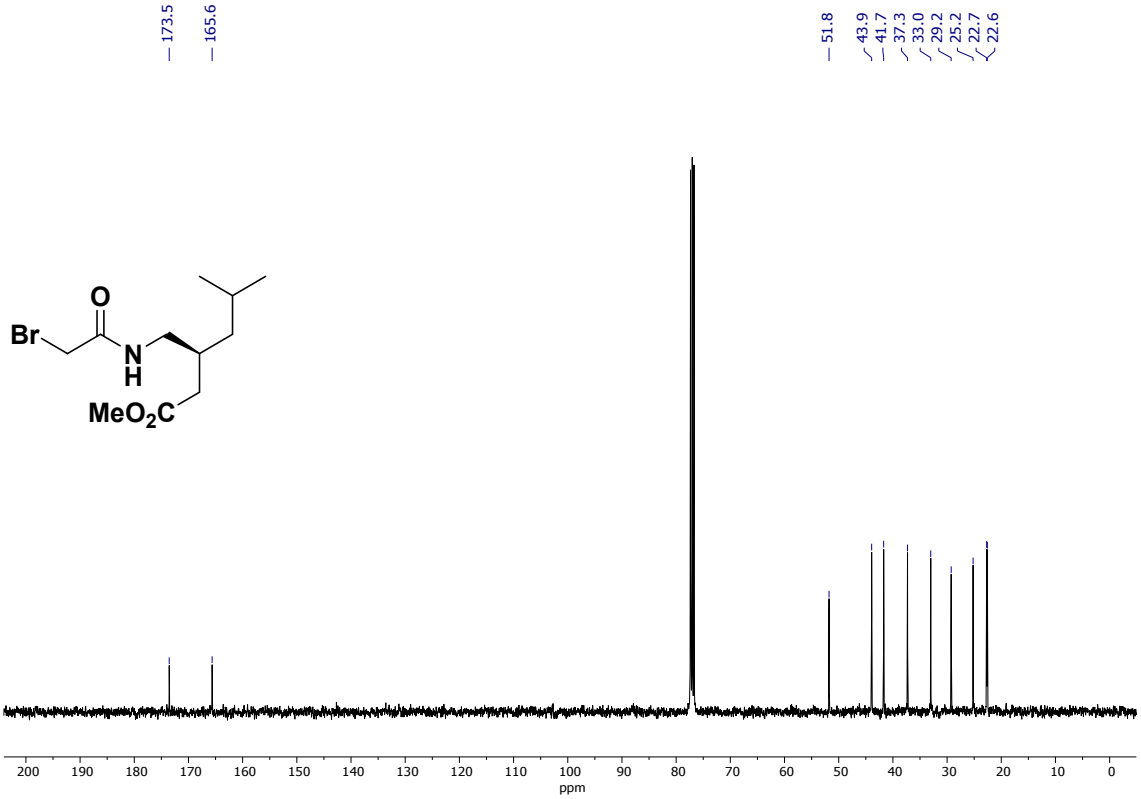


Figure S32. ^{13}C NMR (101 MHz, $CDCl_3$) of **2z**

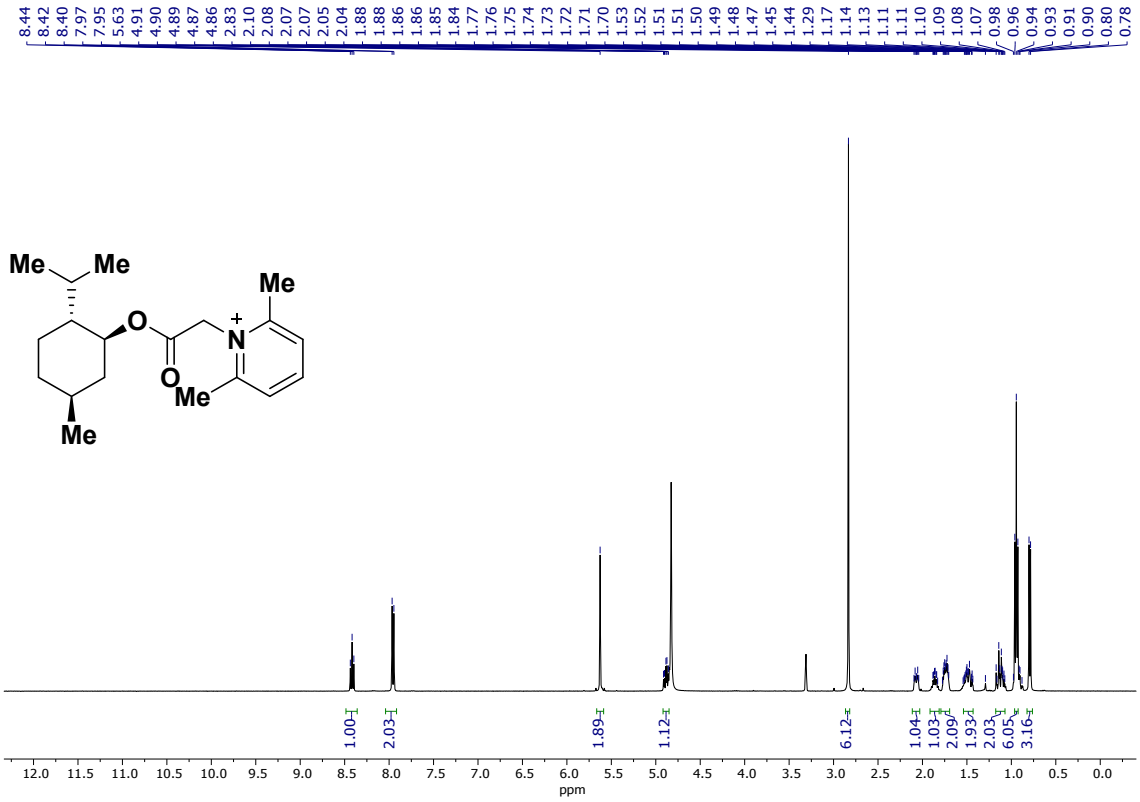


Figure S33. ^{1}H NMR (400 MHz, CD_3OD) of lutidine-alkyl salt

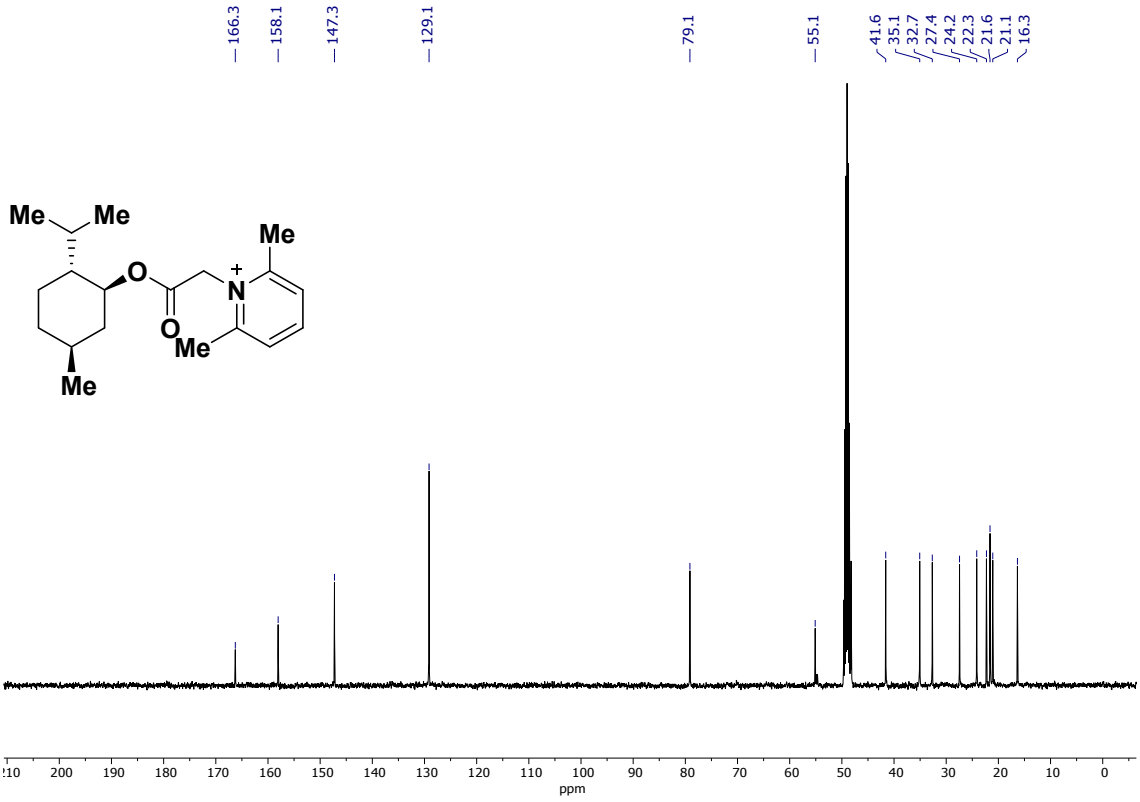


Figure S34. ^{13}C NMR (101 MHz, CD_3OD) of lutidine-alkyl salt

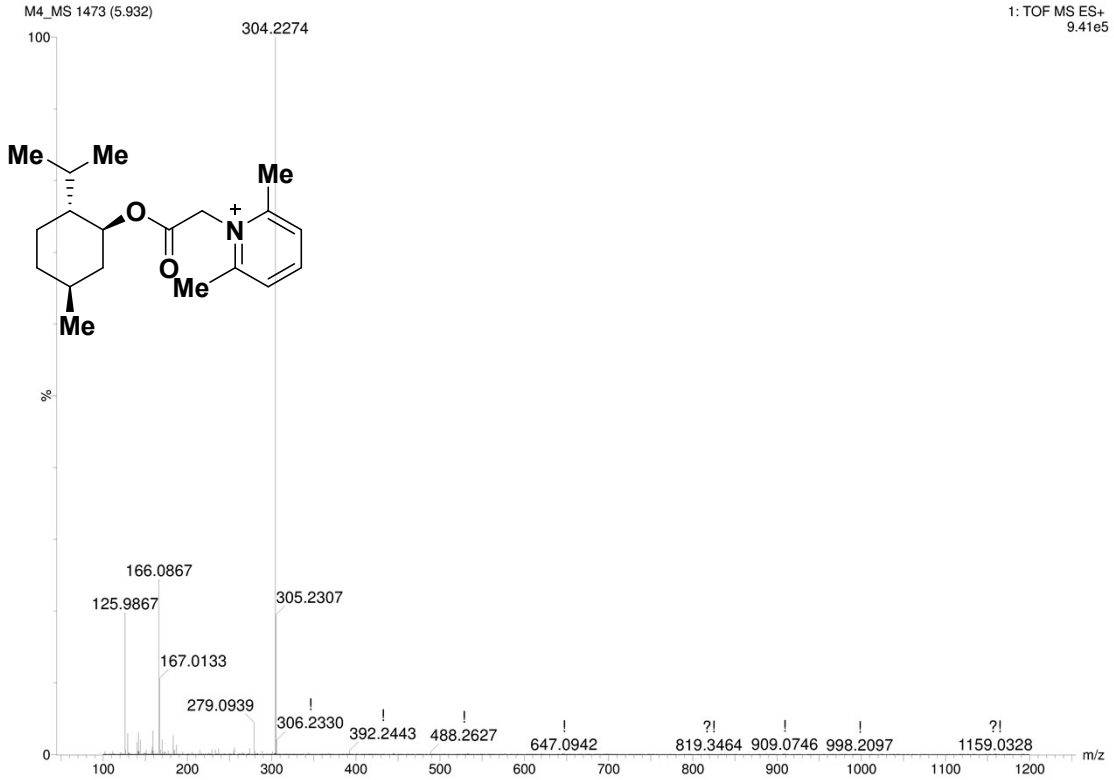


Figure S35. High Resolution Mass Spectra (HRMS) of lutidine-alkyl salt

8.2. Products from catalytic tryptophan C-2 functionalization

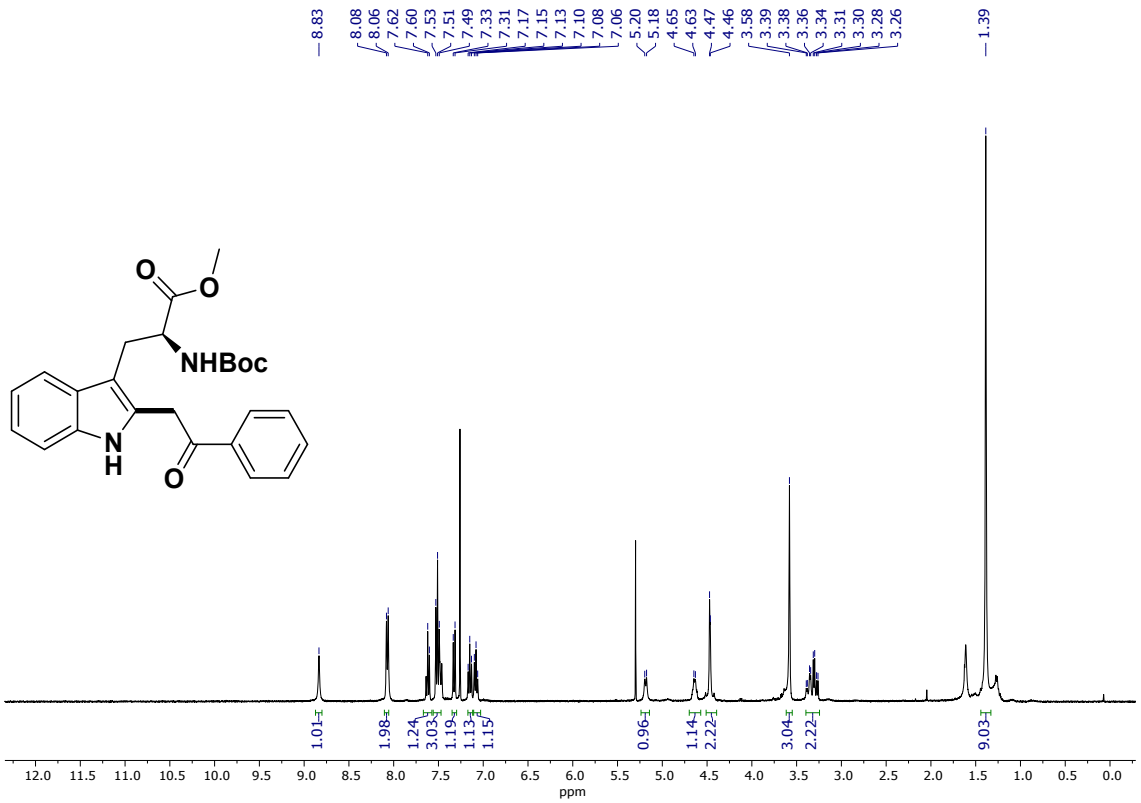


Figure S36. ^{1}H NMR (400 MHz, $CDCl_3$) of **3a**

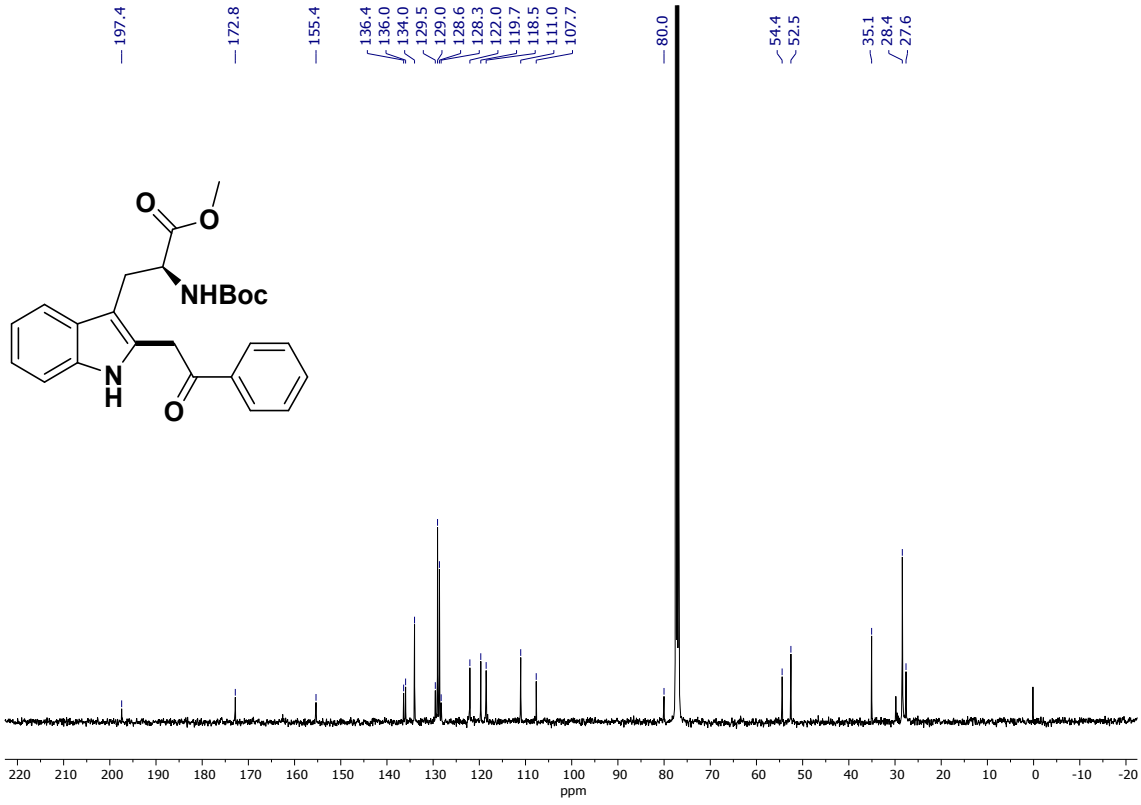


Figure S37. ^{13}C NMR (101 MHz, $CDCl_3$) of **3a**

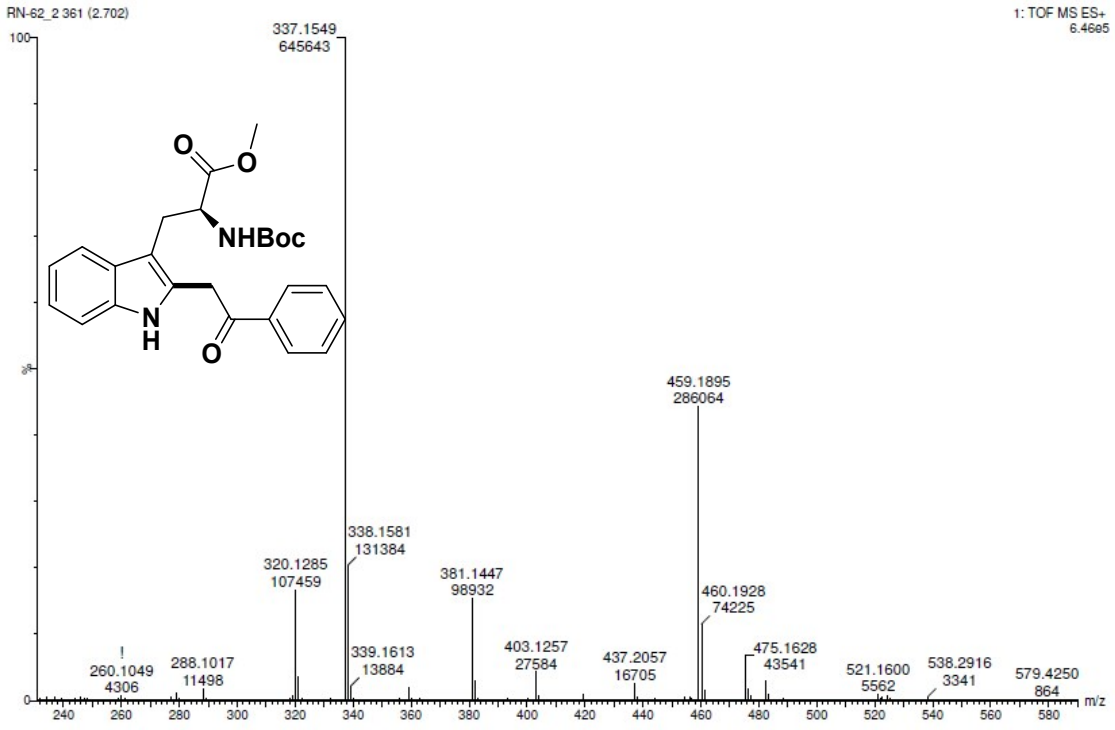


Figure S38. High Resolution Mass Spectra (HRMS) of **3a**

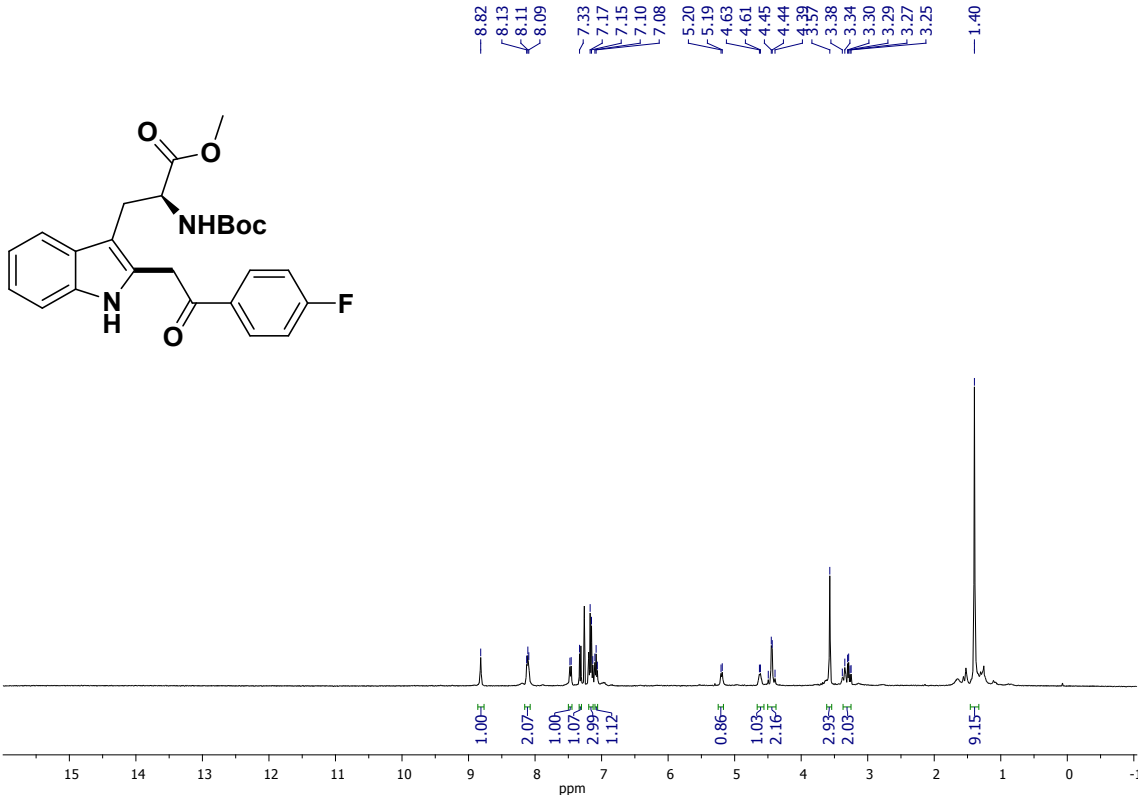


Figure S39. ^{1}H NMR (400 MHz, $CDCl_3$) of **3b**

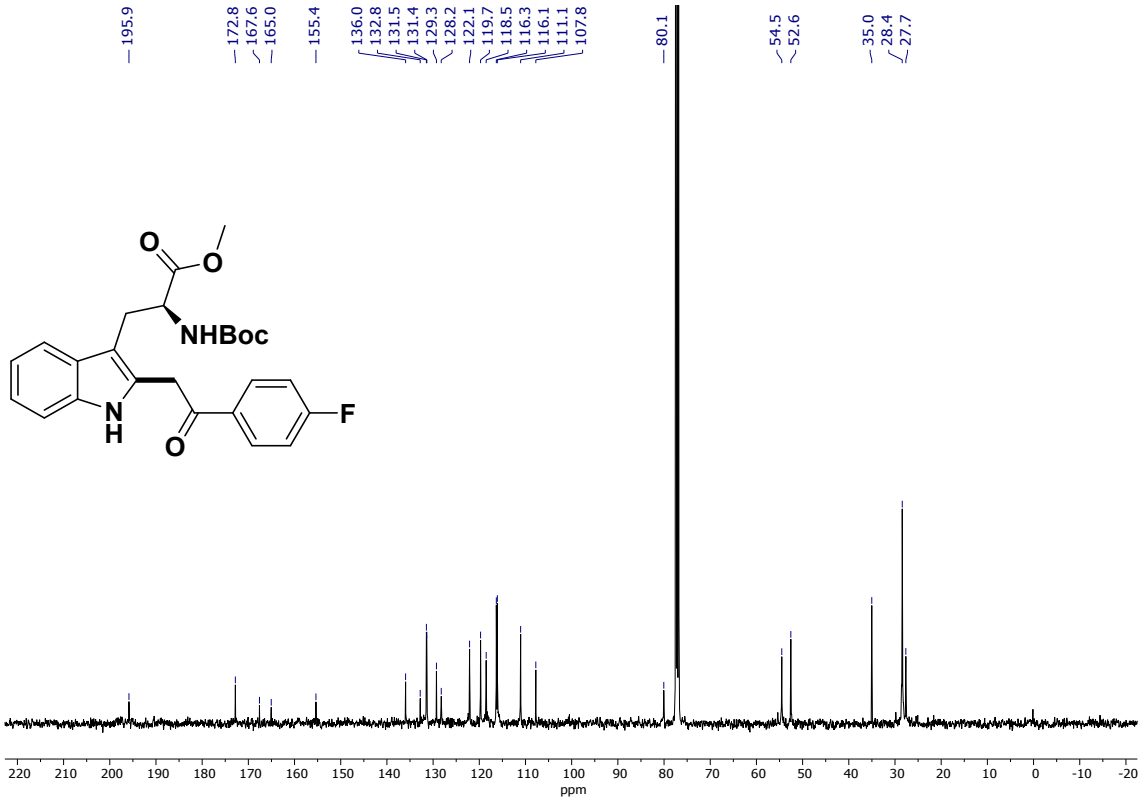


Figure S40. ^{13}C NMR (101 MHz, $CDCl_3$) of **3b**

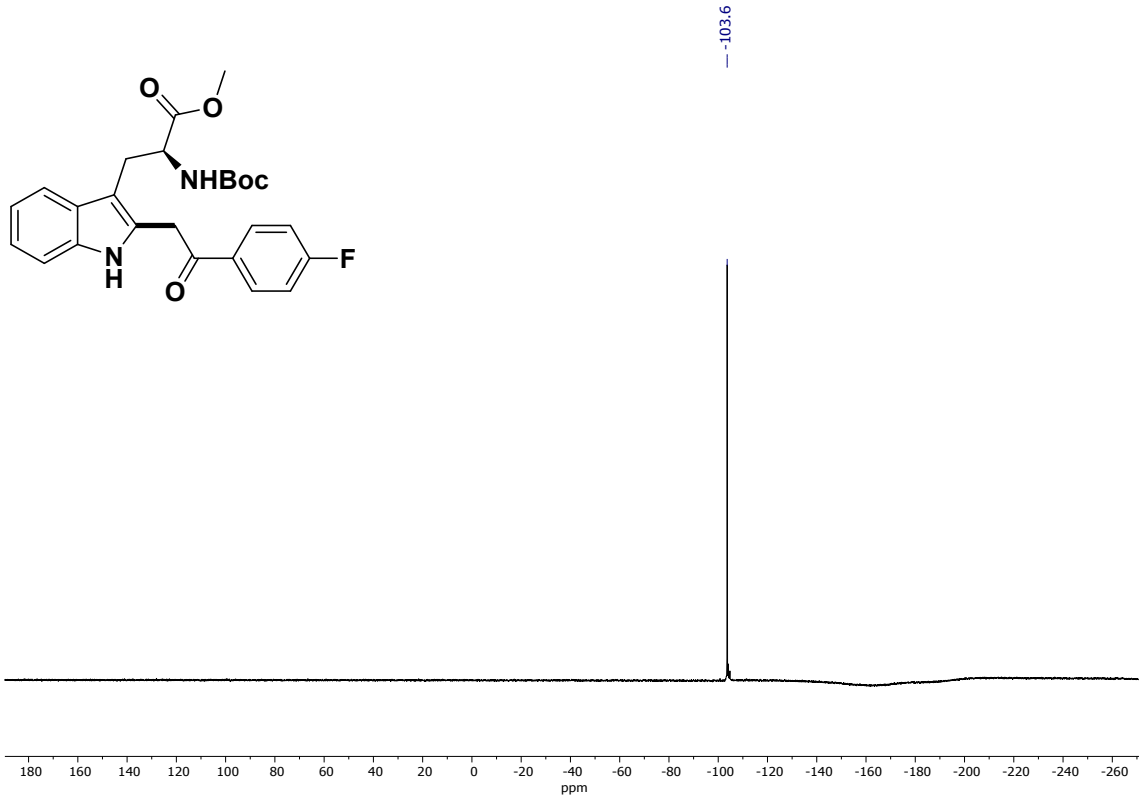


Figure S41. ^{19}F NMR (377 MHz, $CDCl_3$) of **3b**

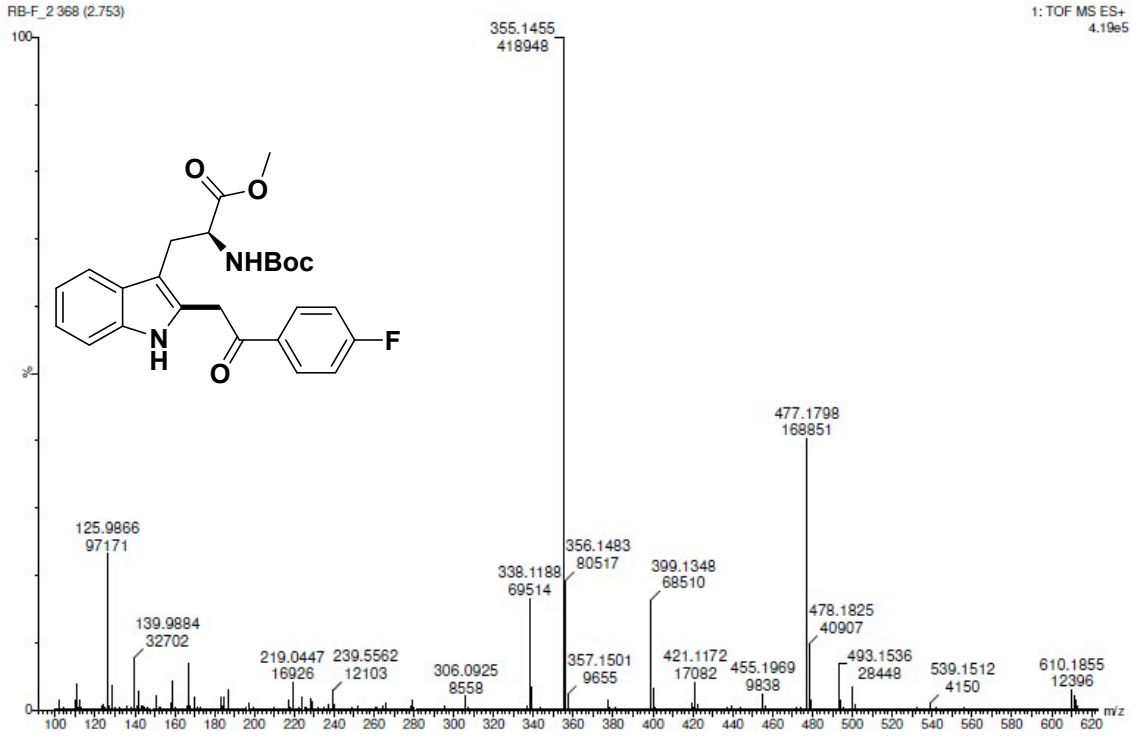


Figure S42. High Resolution Mass Spectra (HRMS) of **3b**

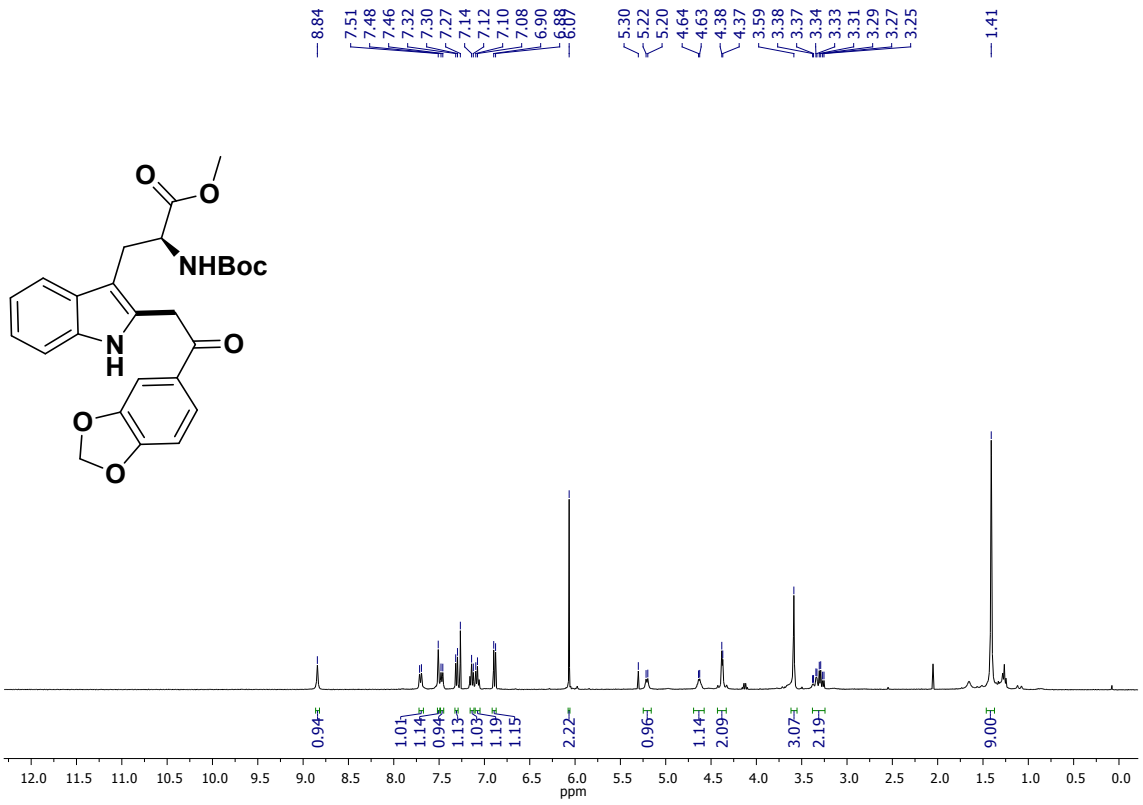


Figure S43. ^{1}H NMR (400 MHz, $CDCl_3$) of **3c**

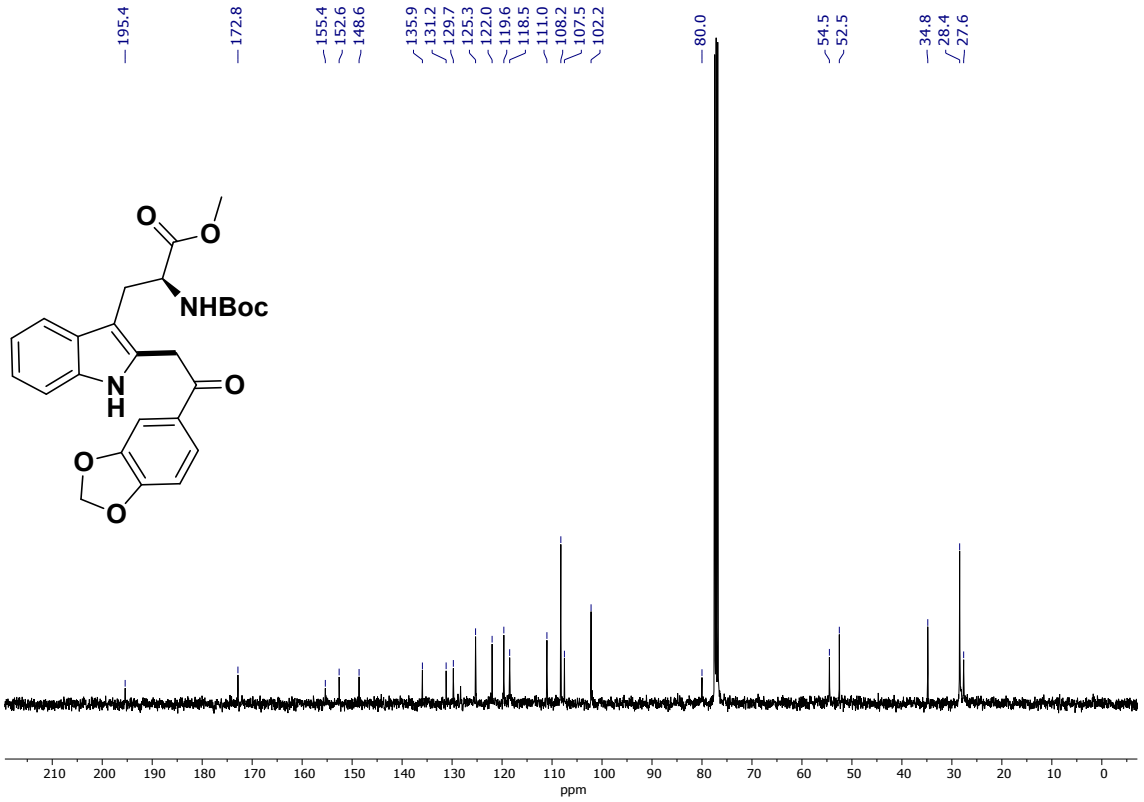


Figure S44. ^{13}C NMR (101 MHz, $CDCl_3$) of **3c**

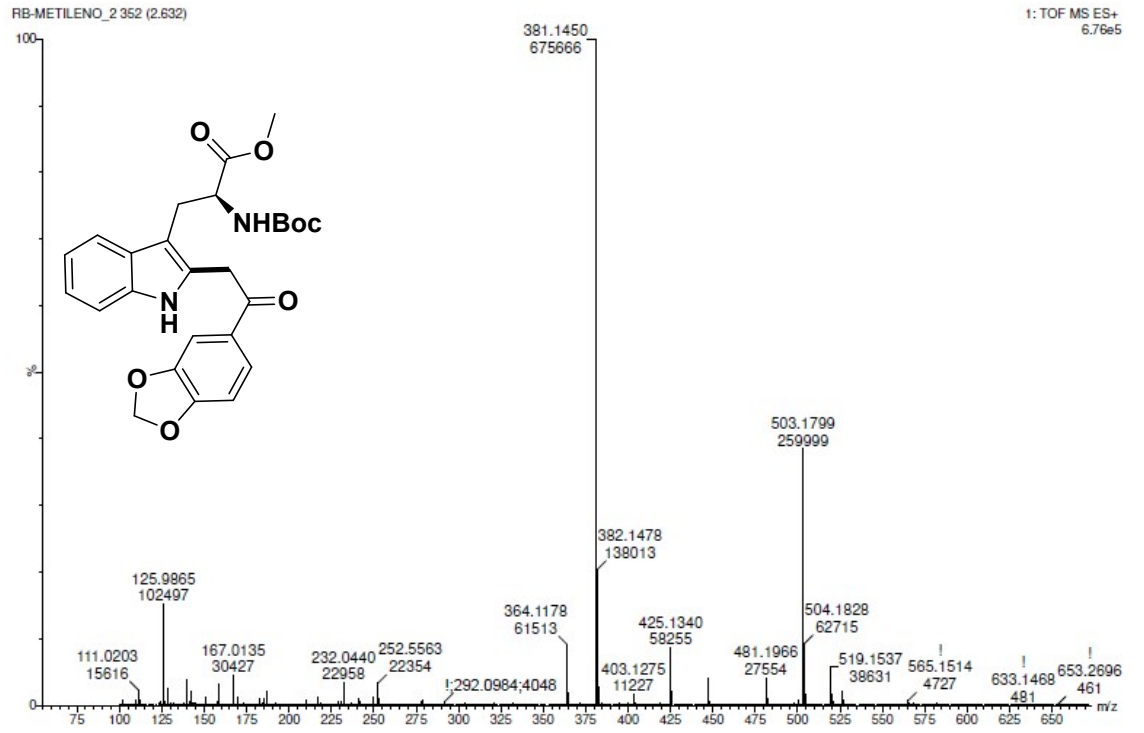


Figure S45. High Resolution Mass Spectra (HRMS) of **3c**

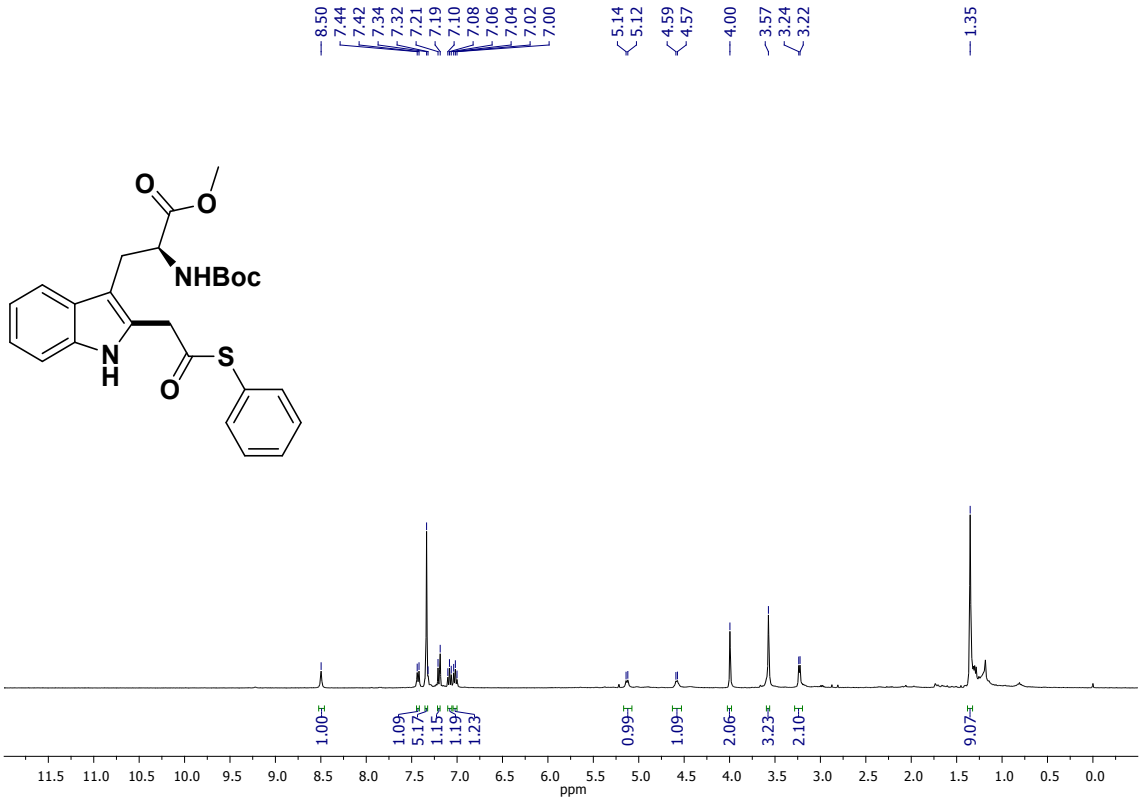


Figure S46. ^{1}H NMR (400 MHz, $CDCl_3$) of **3d**

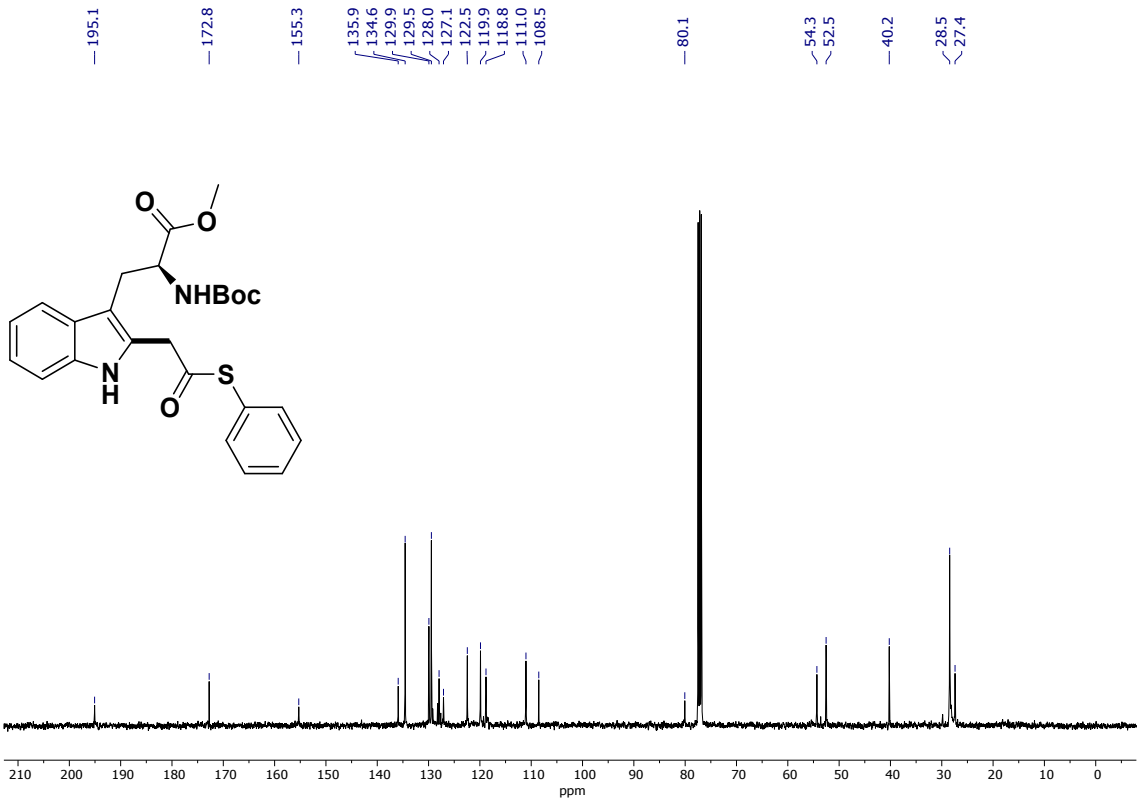


Figure S47. ^{13}C NMR (101 MHz, $CDCl_3$) of **3d**

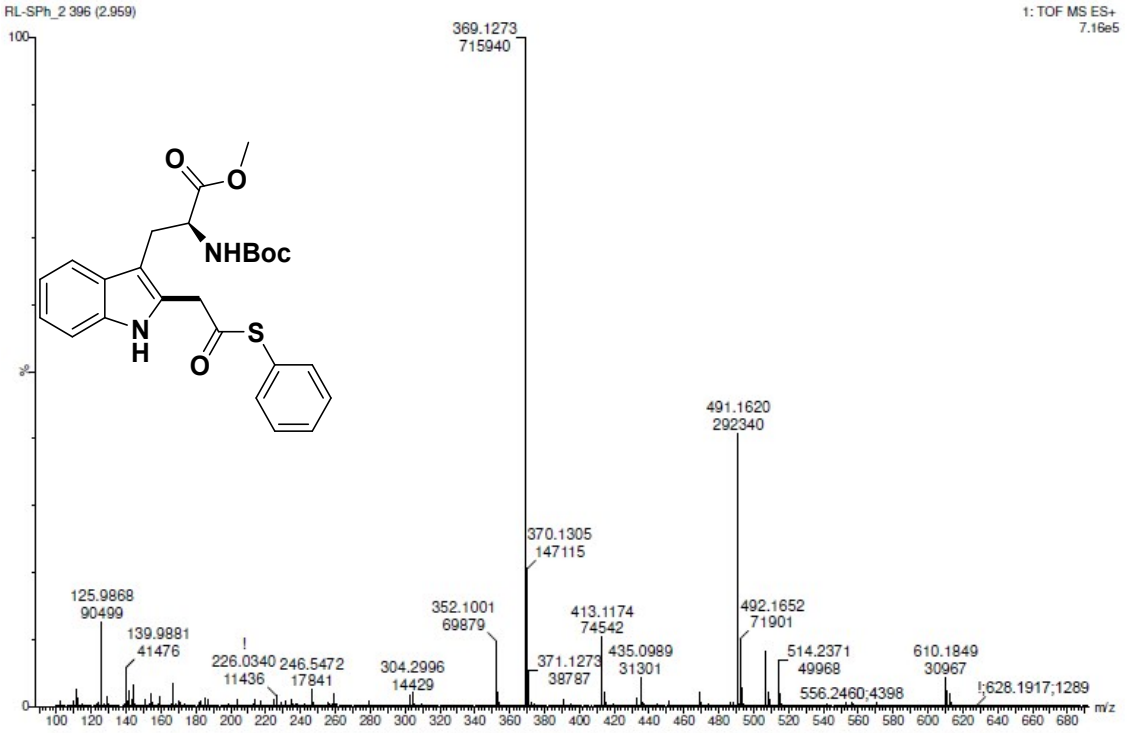


Figure S48. High Resolution Mass Spectra (HRMS) of **3d**

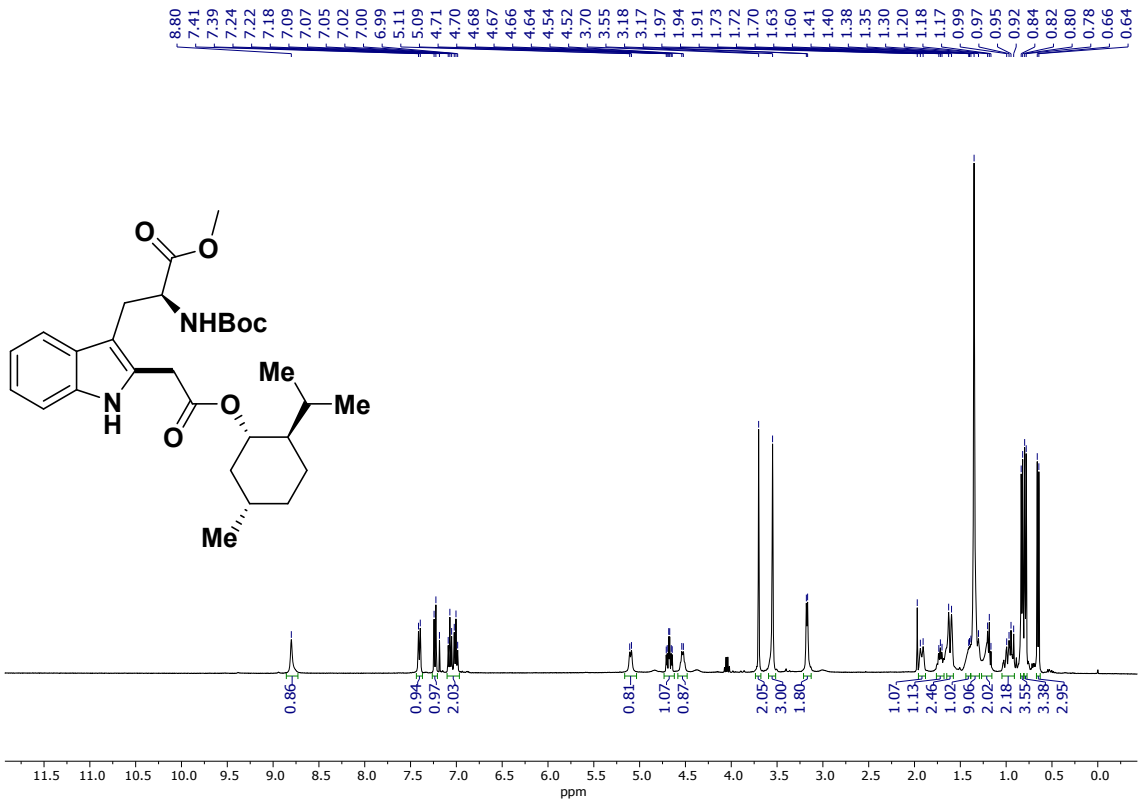


Figure S49. ^{1}H NMR (400 MHz, $CDCl_3$) of **3e**

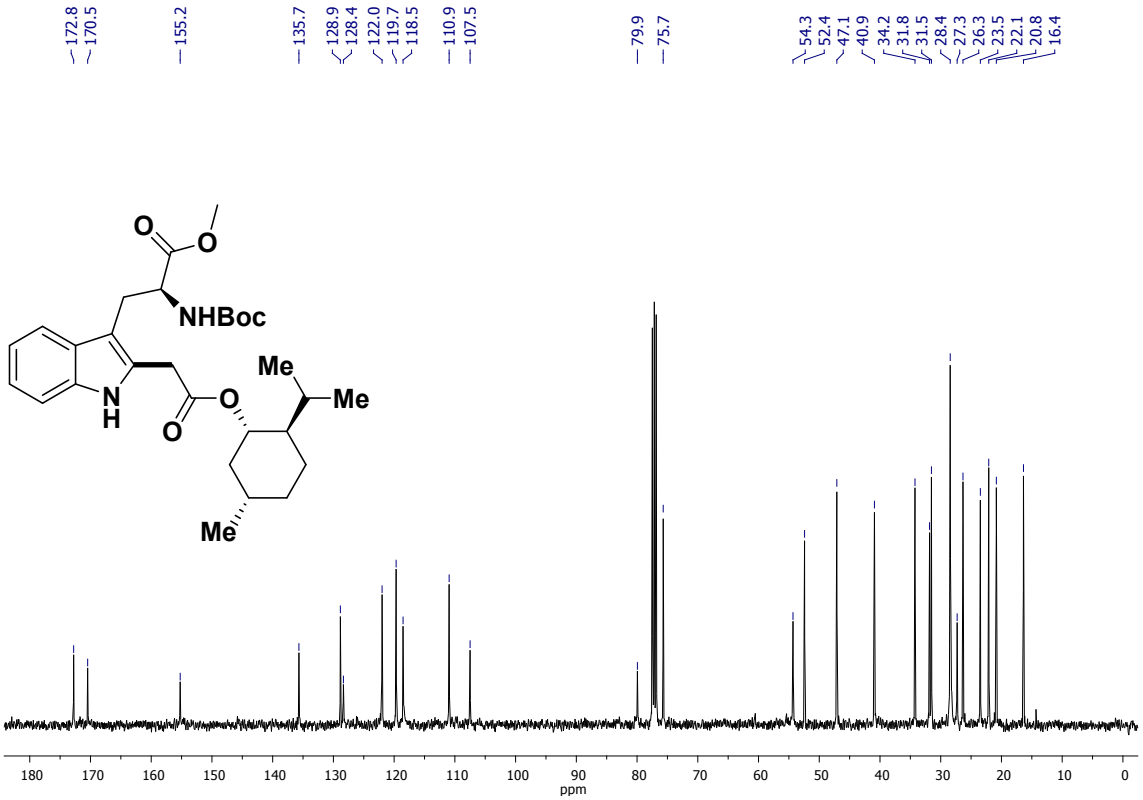


Figure S50. ^{13}C NMR (101 MHz, $CDCl_3$) of **3e**

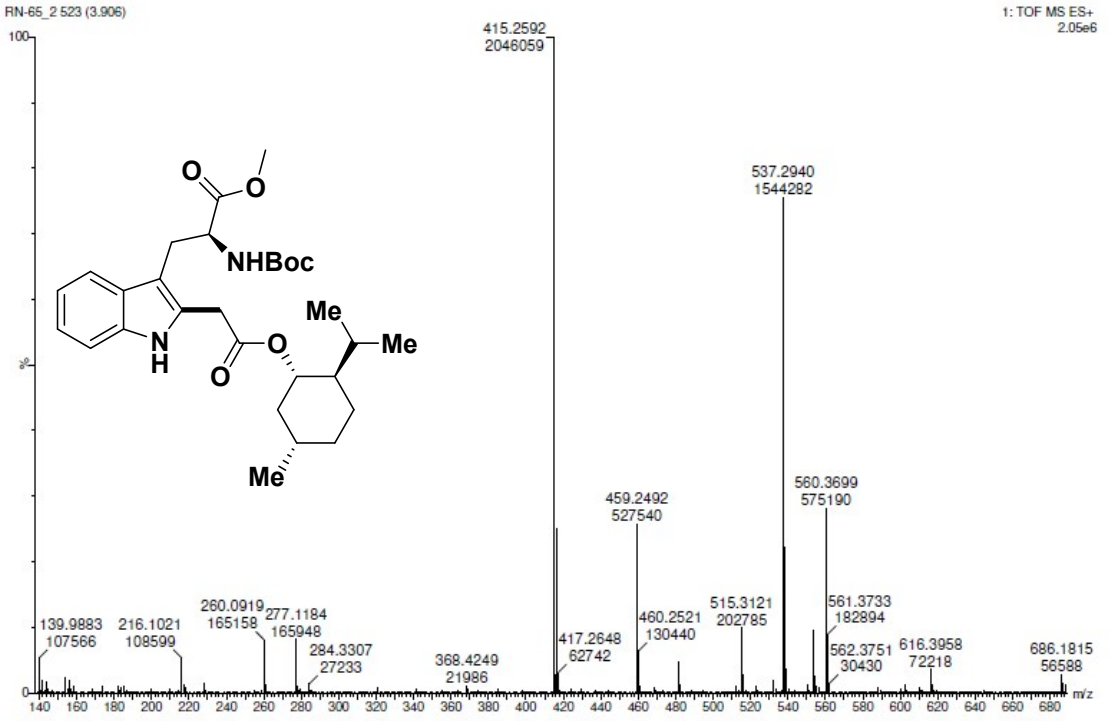


Figure S51. High Resolution Mass Spectra (HRMS) of **3e**

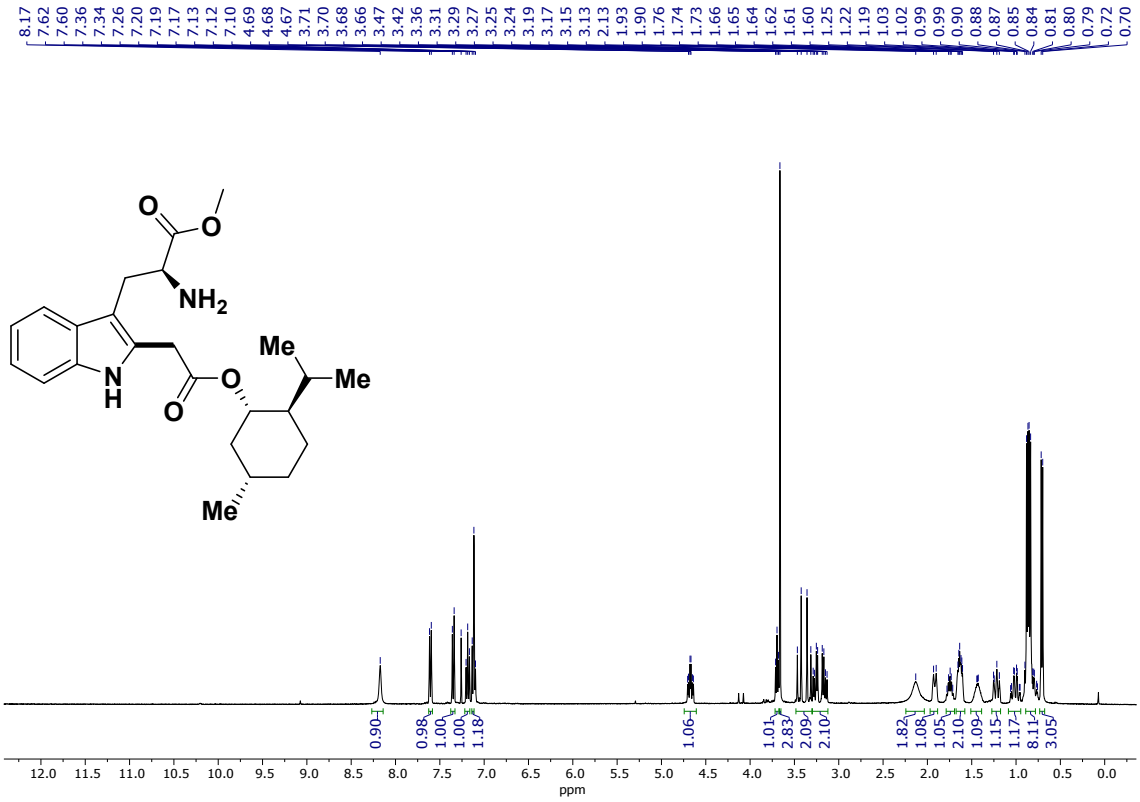


Figure S52. ^{1}H NMR (400 MHz, $CDCl_3$) of **3e**[b]

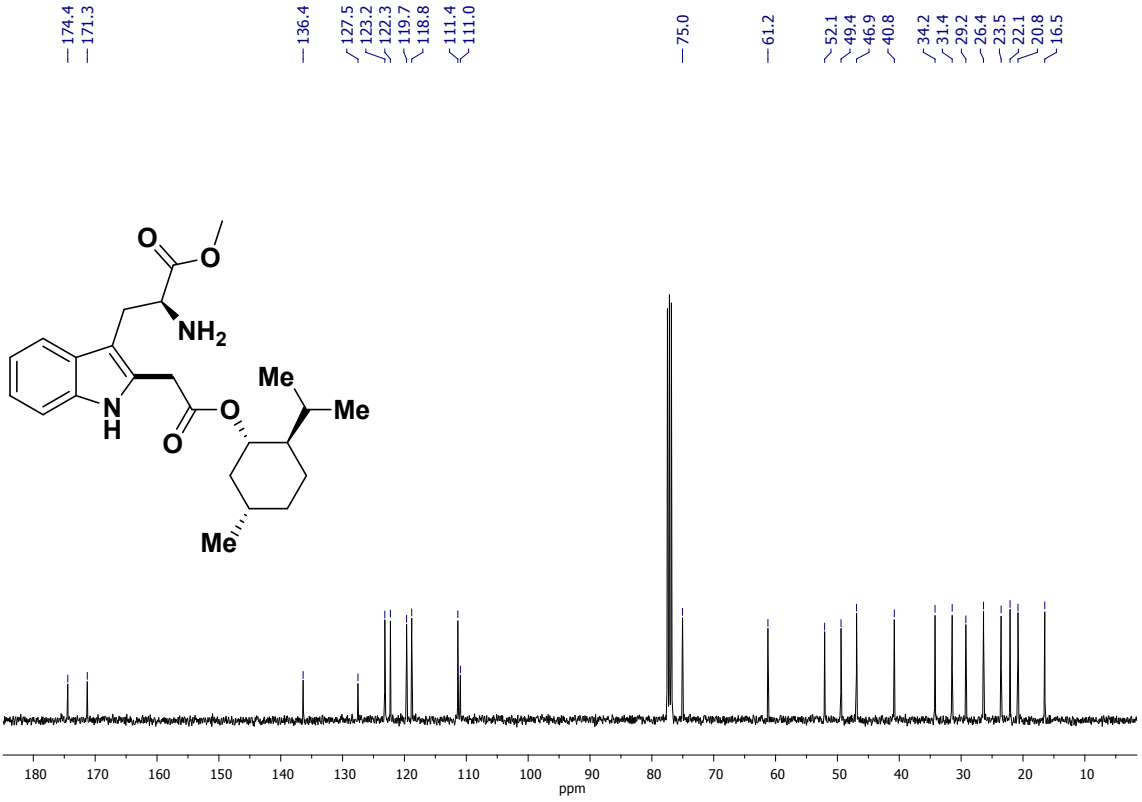


Figure S53. ^{13}C NMR (101 MHz, $CDCl_3$) of **3e**[b]

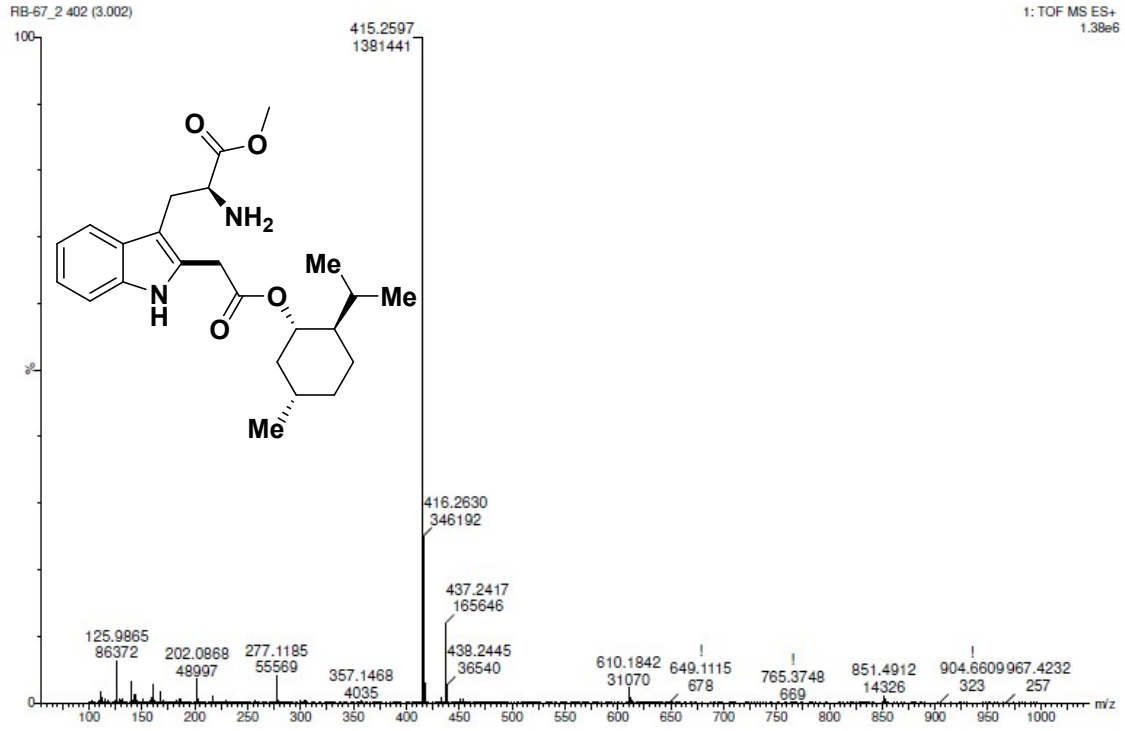


Figure S54. High Resolution Mass Spectra (HRMS) of **3e**[b]

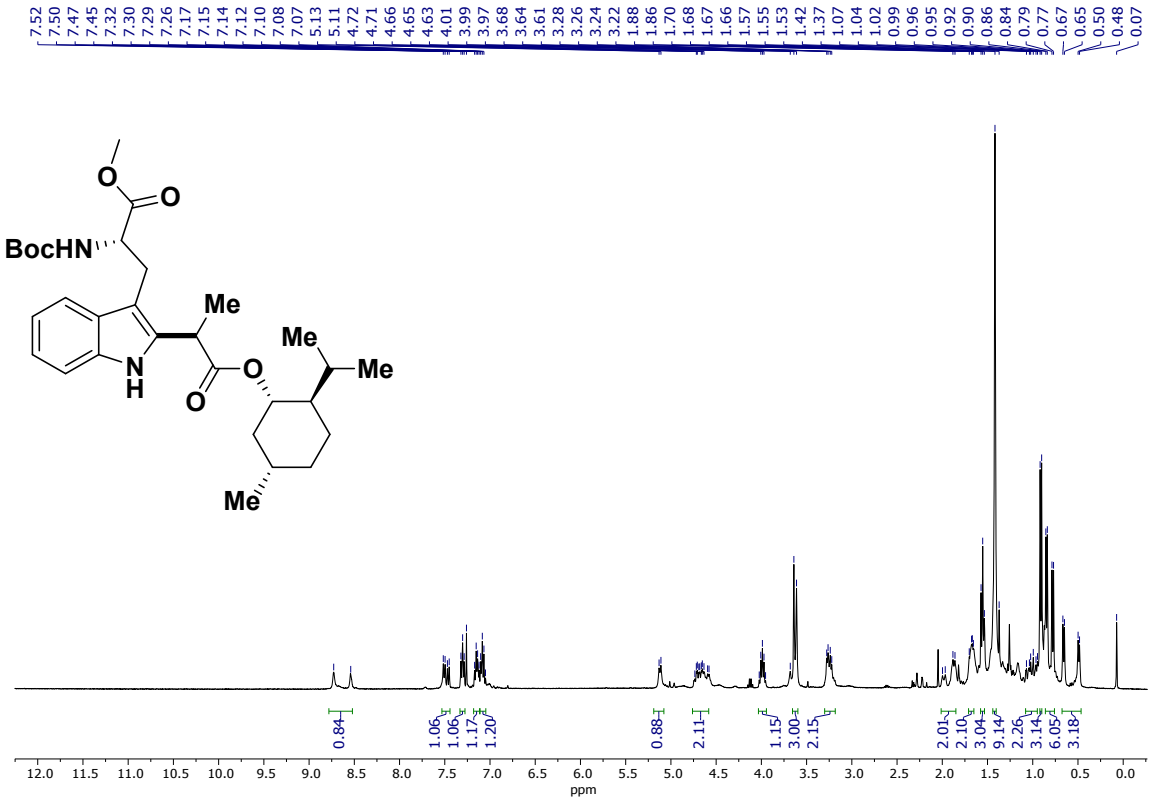


Figure S55. ^{1}H NMR (400 MHz, $CDCl_3$) of **3f**

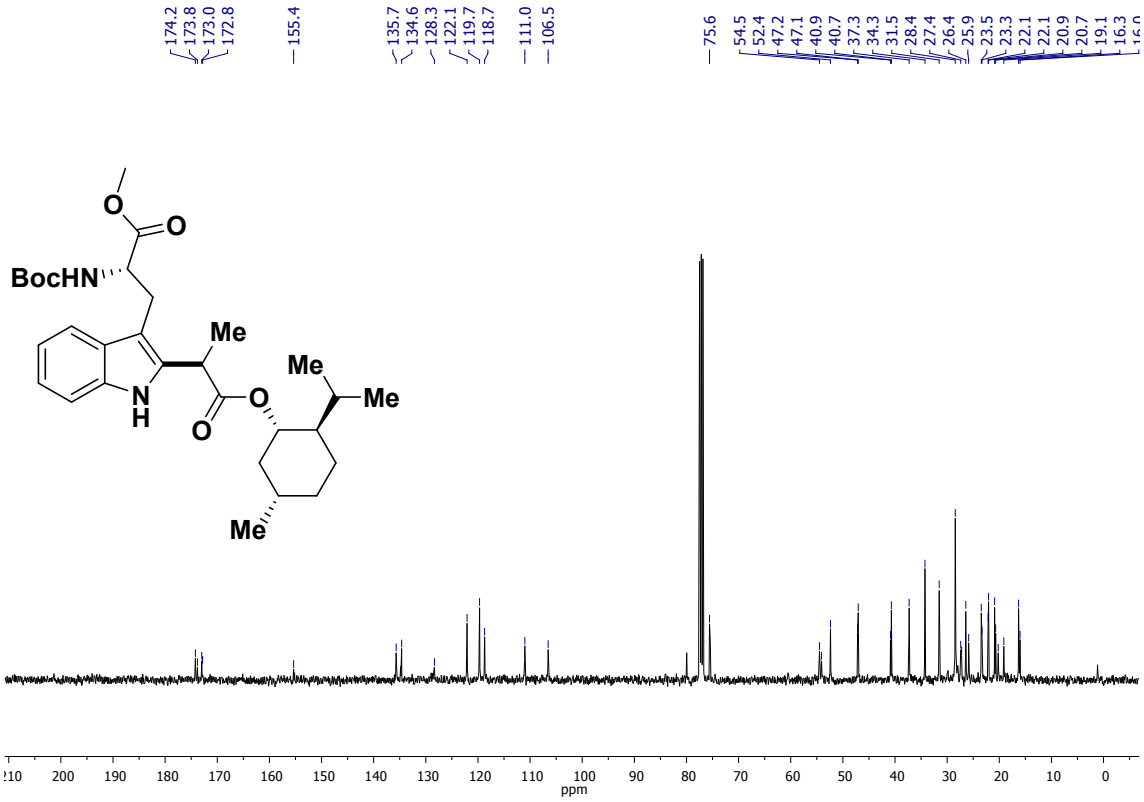


Figure S56. ^{13}C NMR (101 MHz, $CDCl_3$) of **3f**

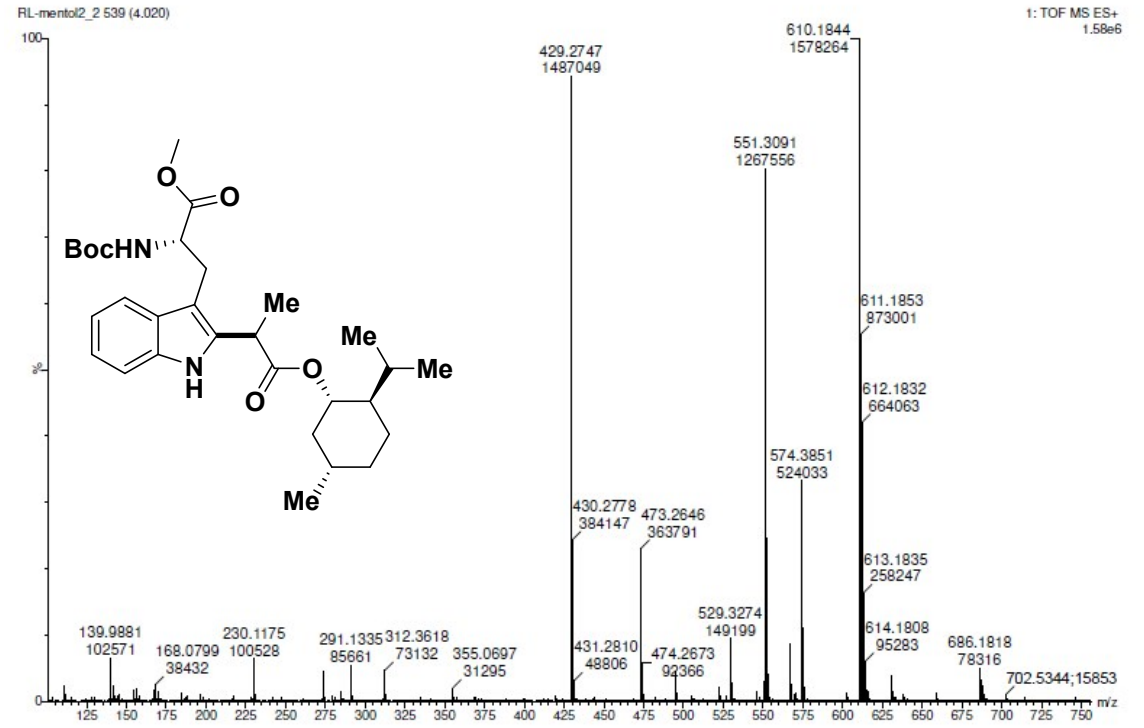


Figure S57. High Resolution Mass Spectra (HRMS) of **3f**

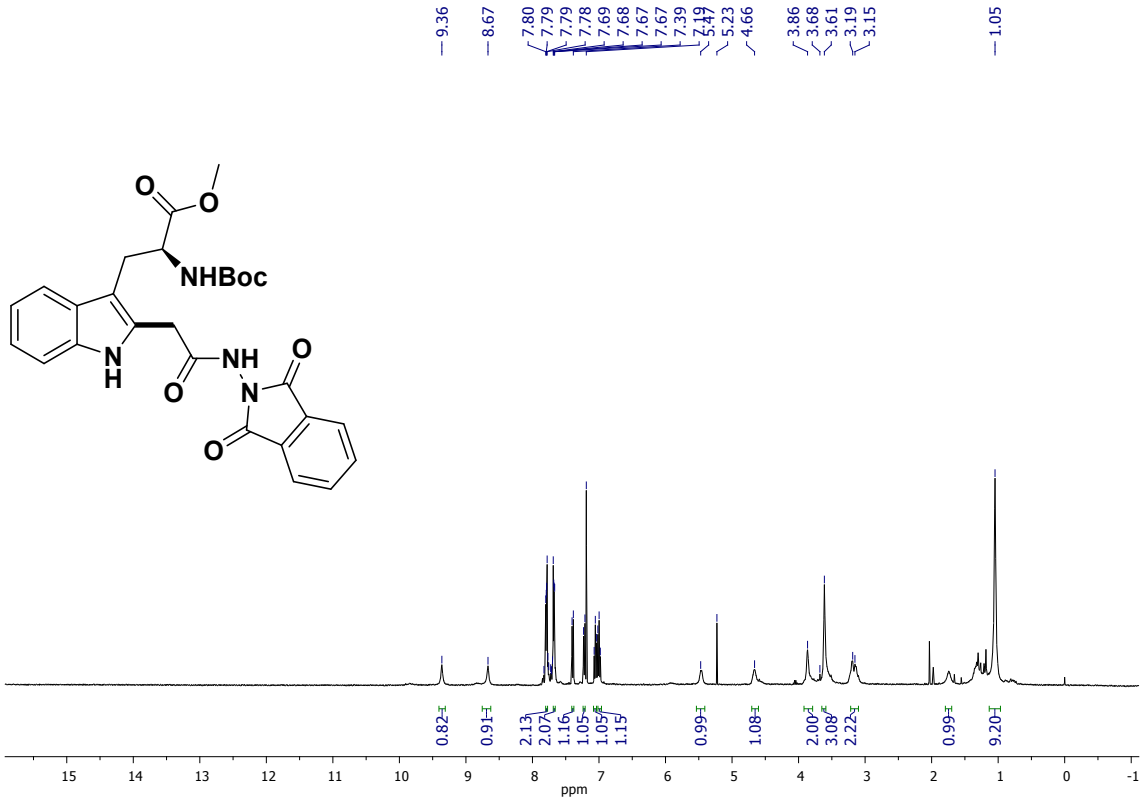


Figure S58. ^{1}H NMR (400 MHz, $CDCl_3$) of **3g**

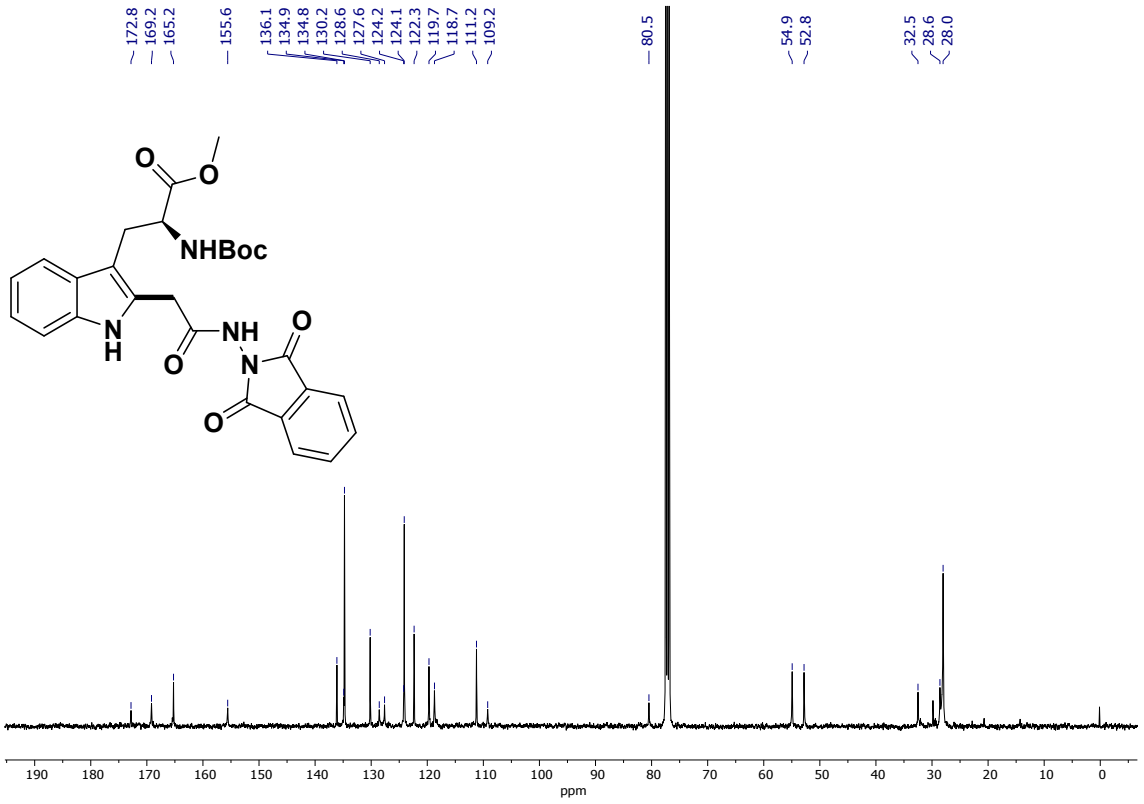


Figure S59. ^{13}C NMR (101 MHz, $CDCl_3$) of **3g**

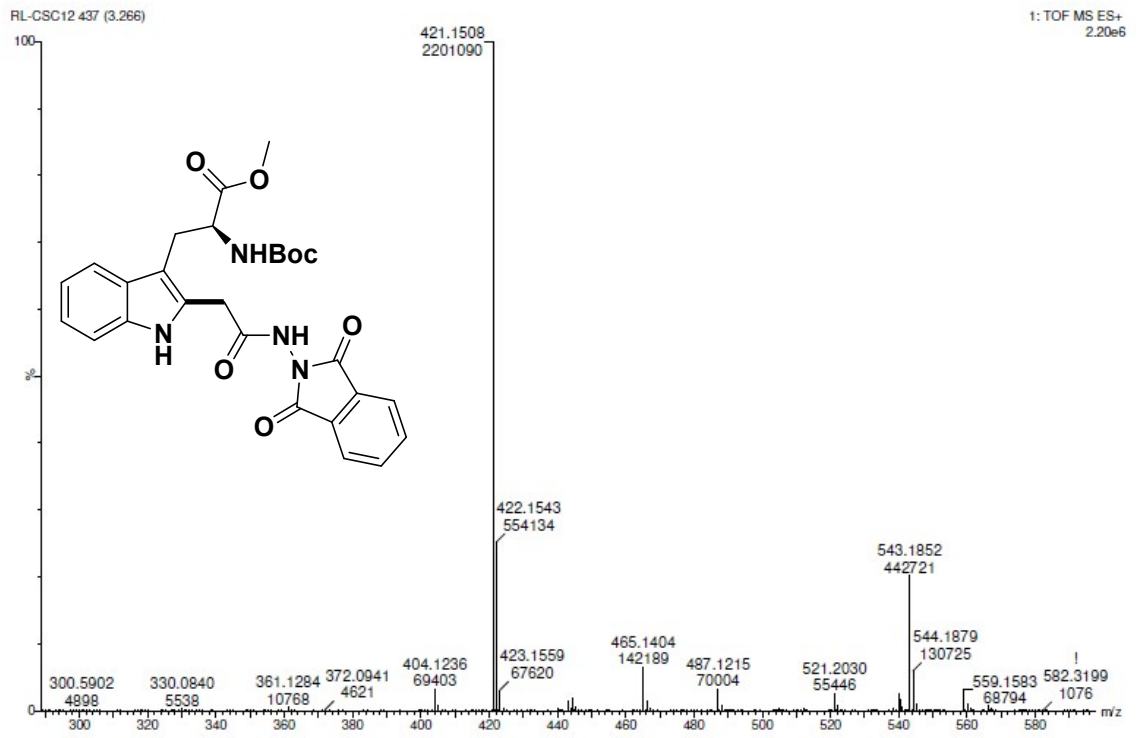


Figure S60. High Resolution Mass Spectra (HRMS) of **3g**

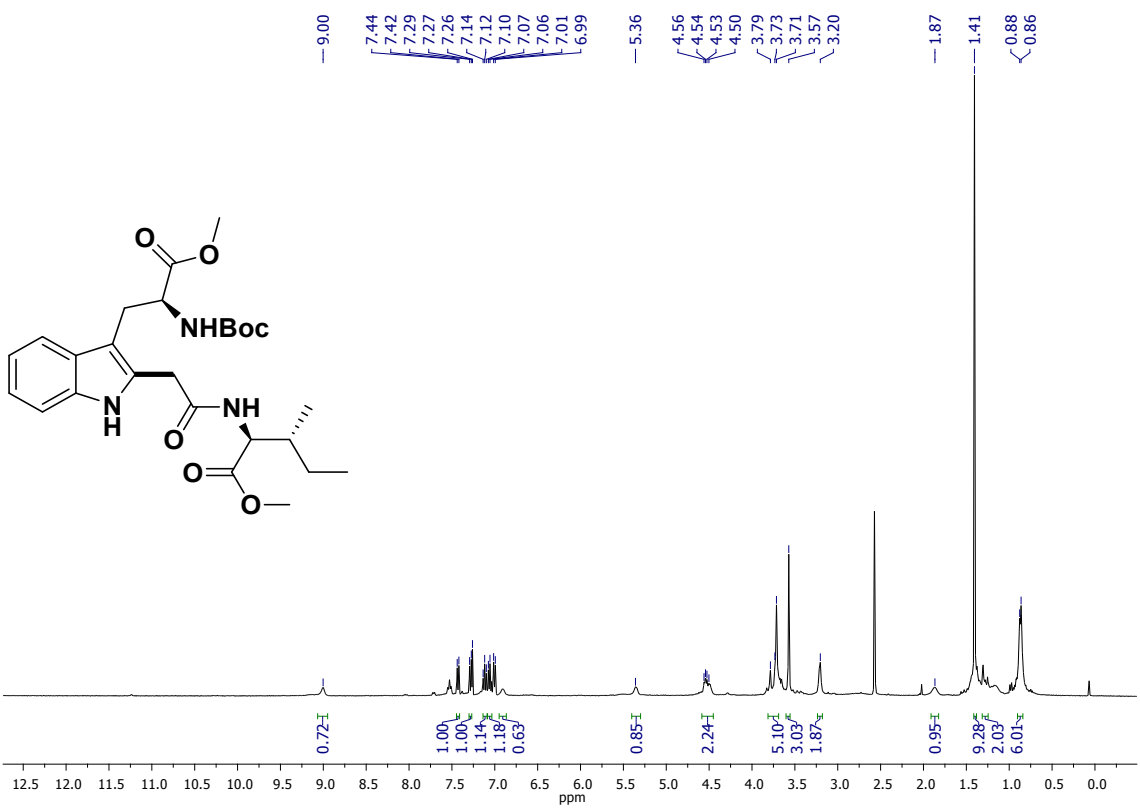


Figure S61. ^{1}H NMR (400 MHz, $CDCl_3$) of **3i**

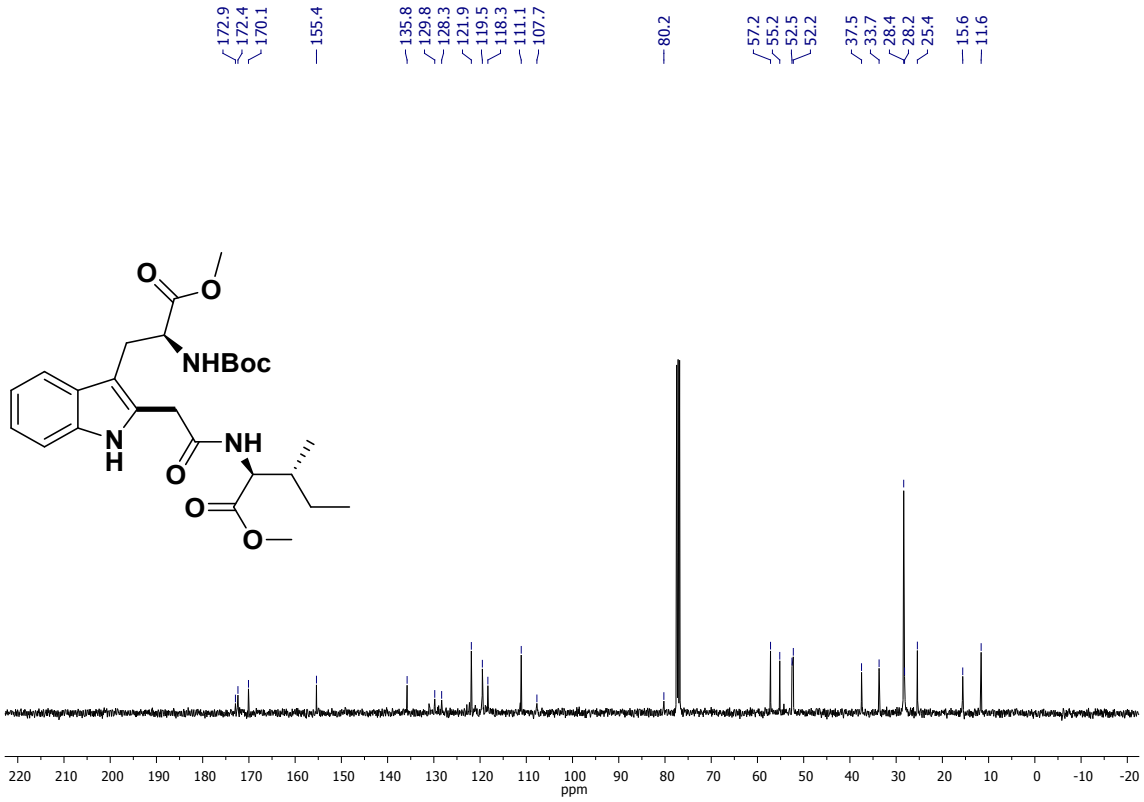


Figure S62. ^{13}C NMR (101 MHz, $CDCl_3$) of **3i**

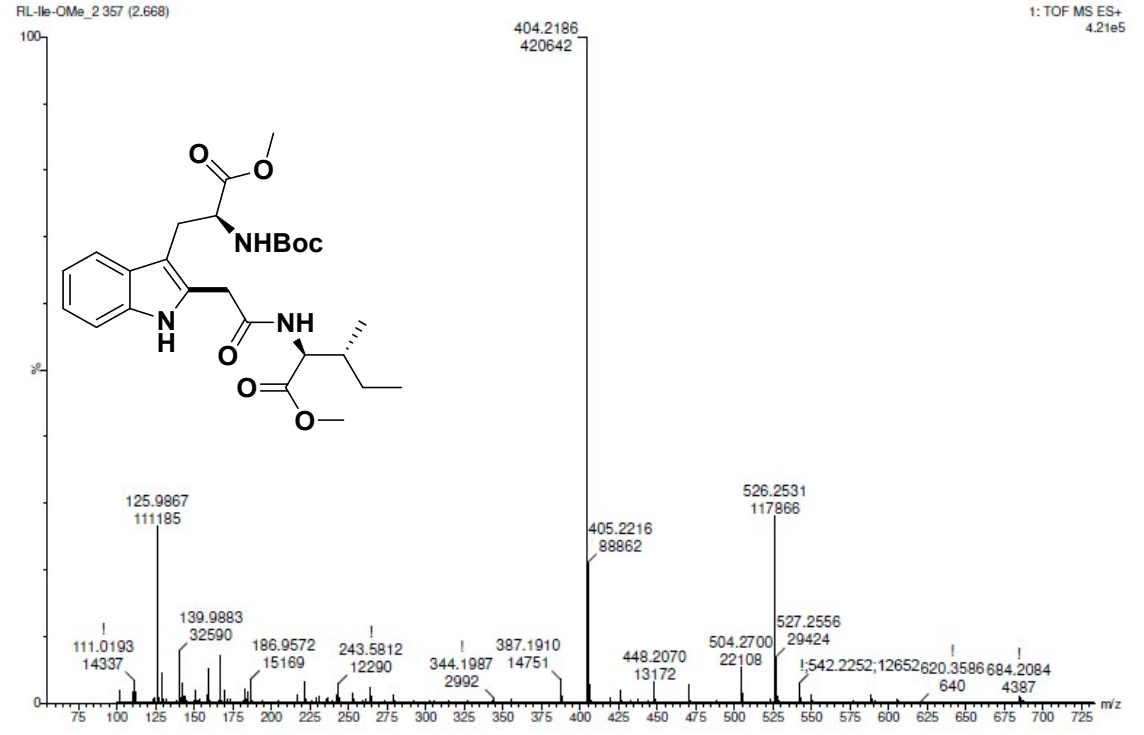


Figure S63. High Resolution Mass Spectra (HRMS) of **3i**

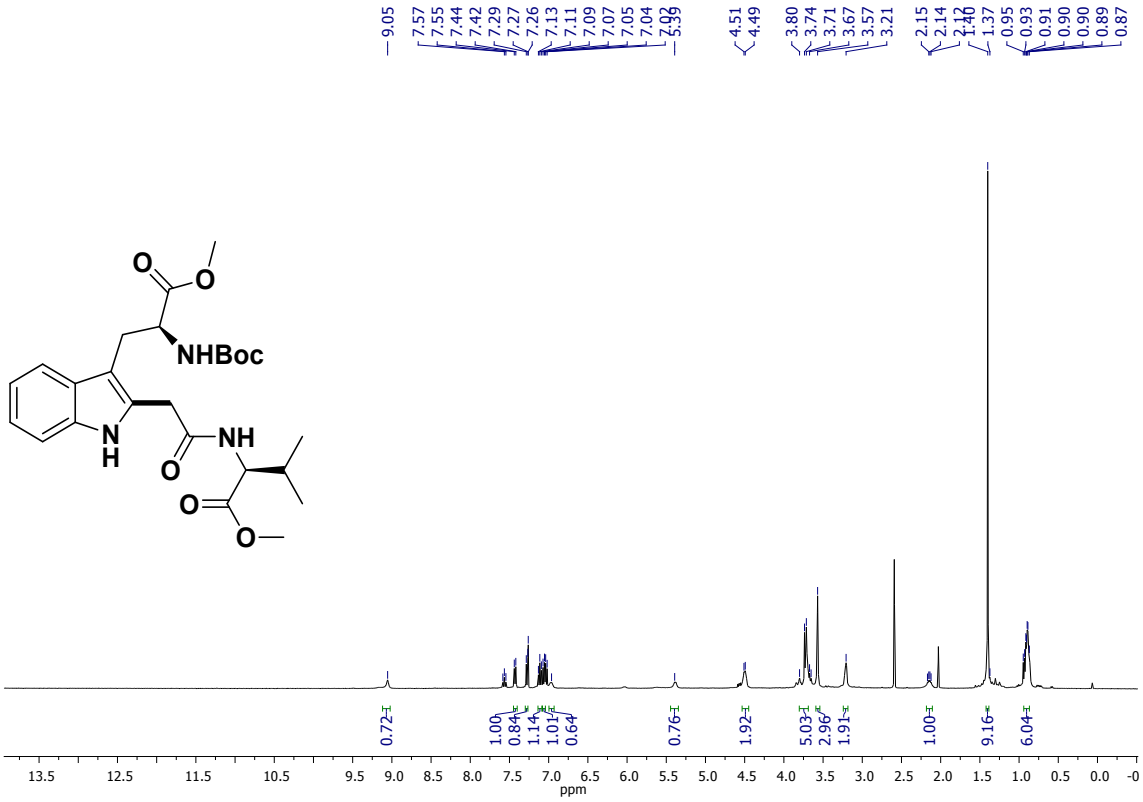


Figure S64. ^{1}H NMR (400 MHz, $CDCl_3$) of **3j**

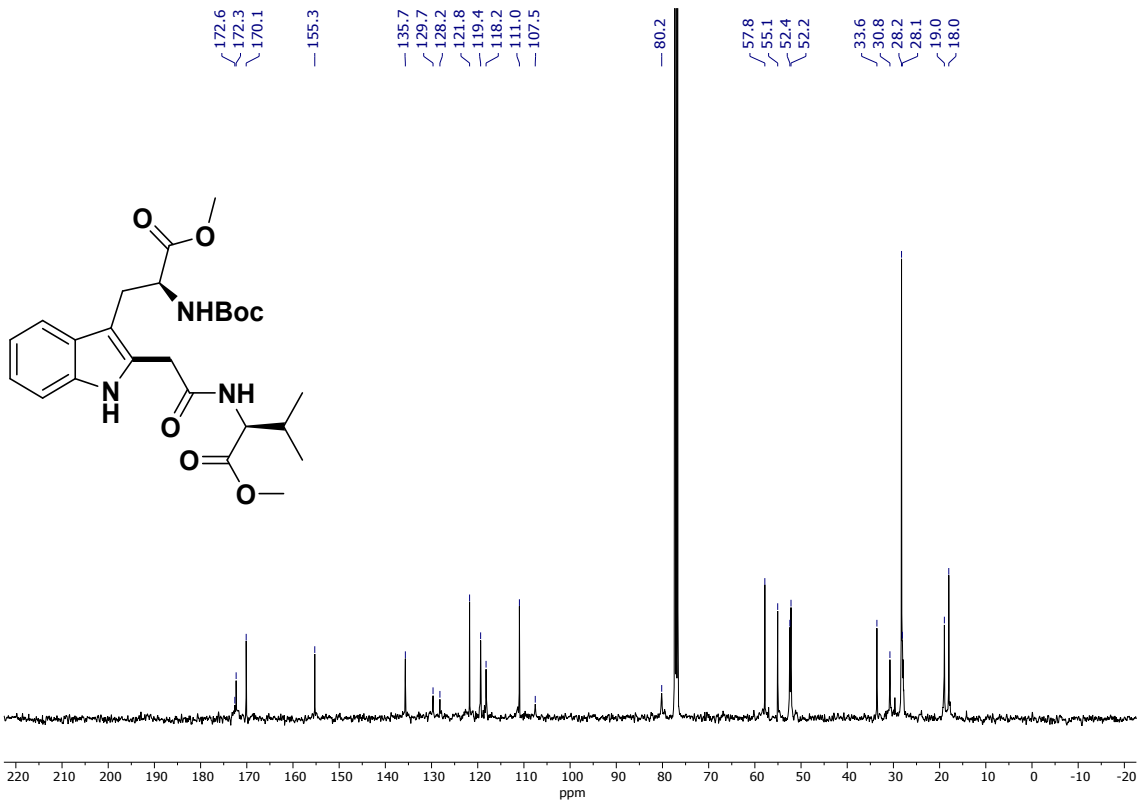


Figure S65. ^{13}C NMR (101 MHz, $CDCl_3$) of **3j**

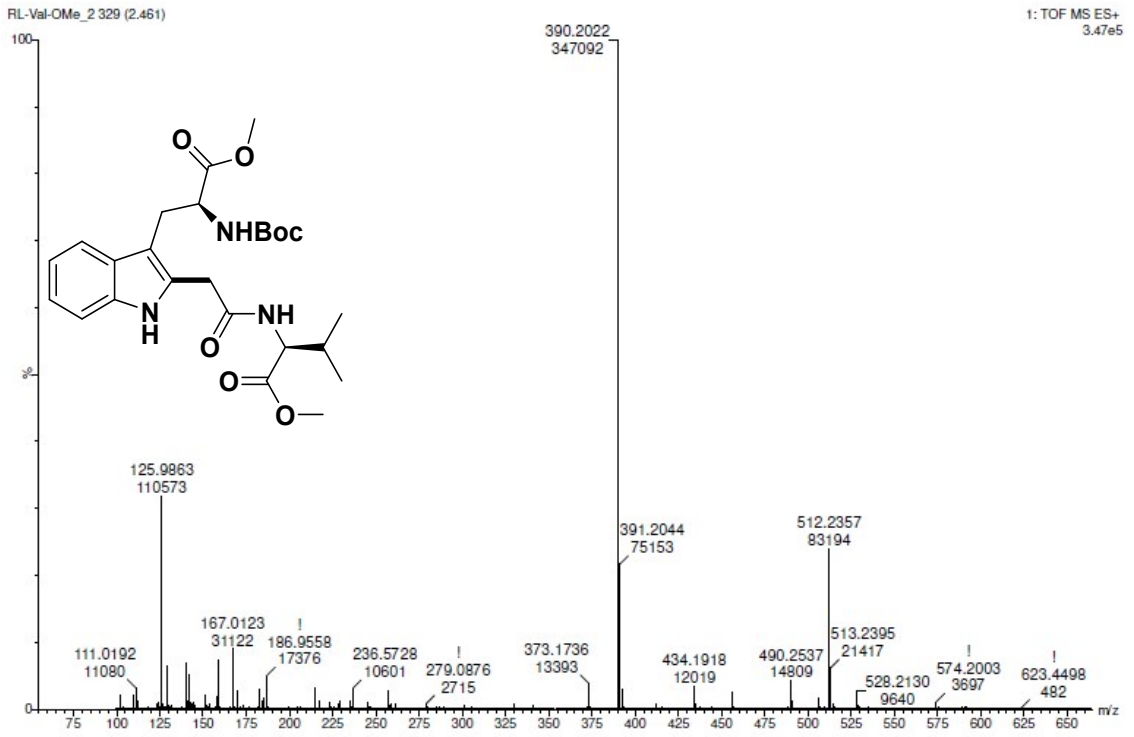


Figure S66. High Resolution Mass Spectra (HRMS) of **3j**

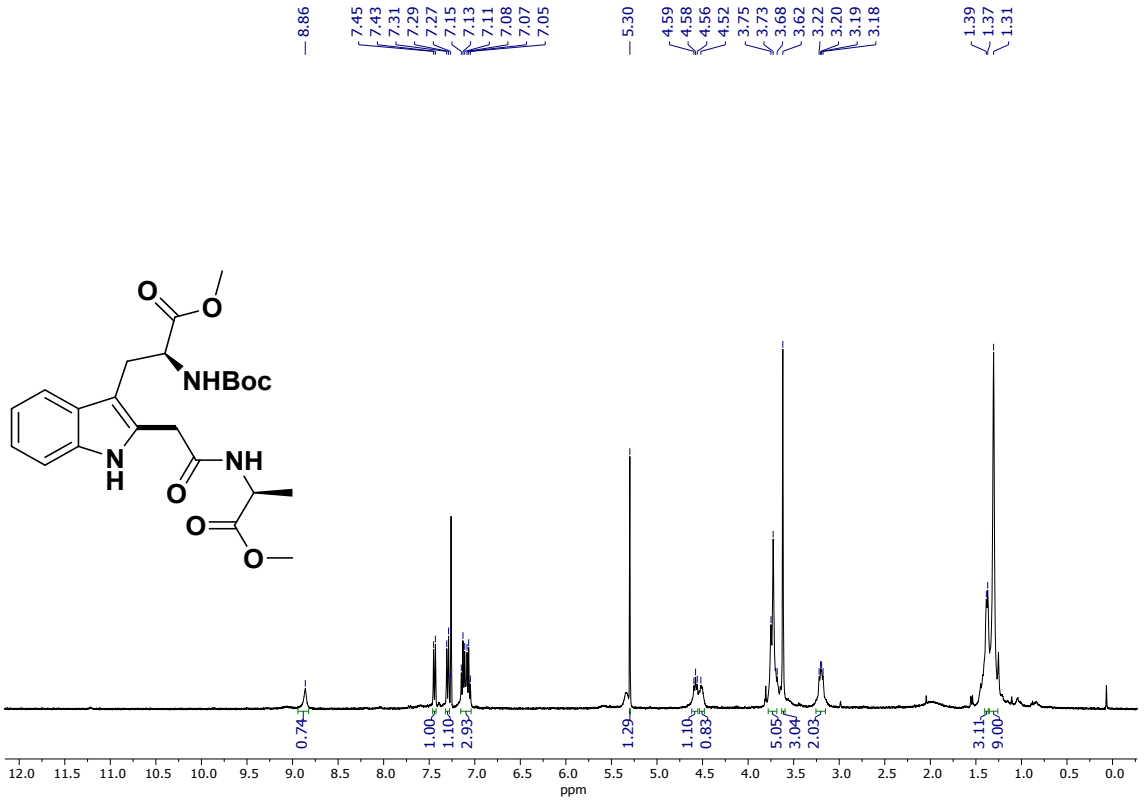


Figure S67. ^{1}H NMR (400 MHz, $CDCl_3$) of **3k**

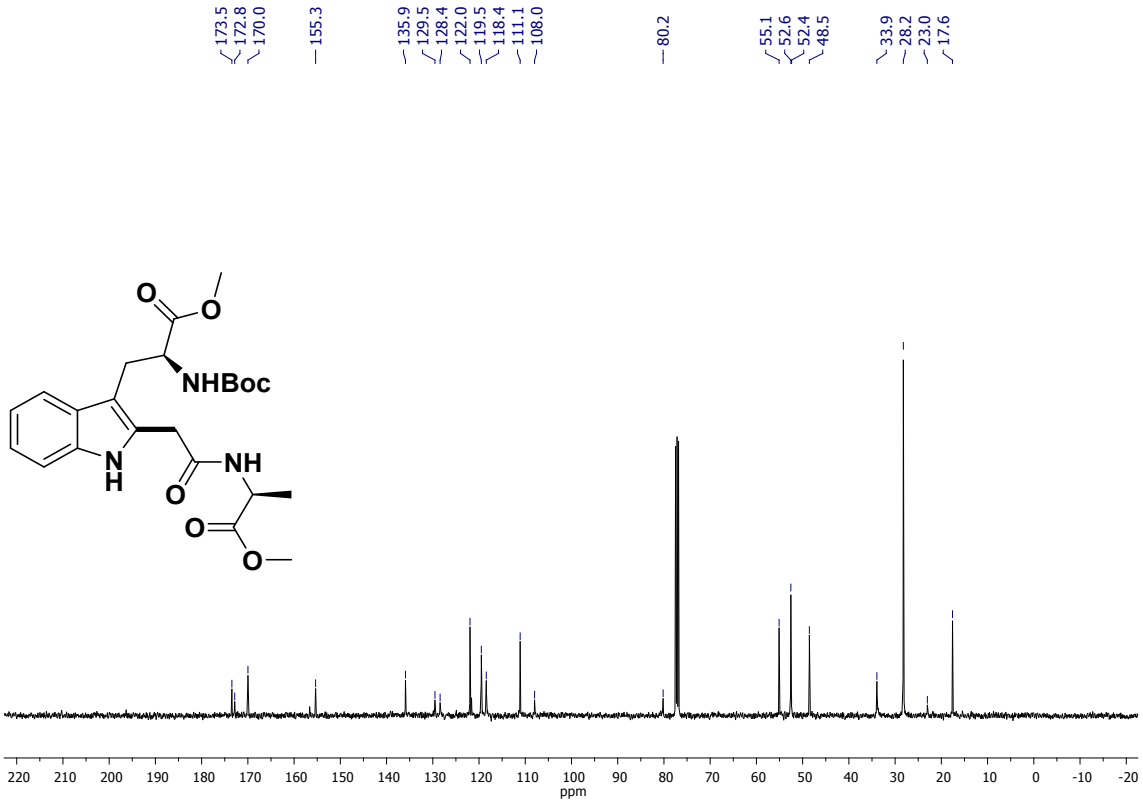


Figure S68. ^{13}C NMR (101 MHz, $CDCl_3$) of **3k**

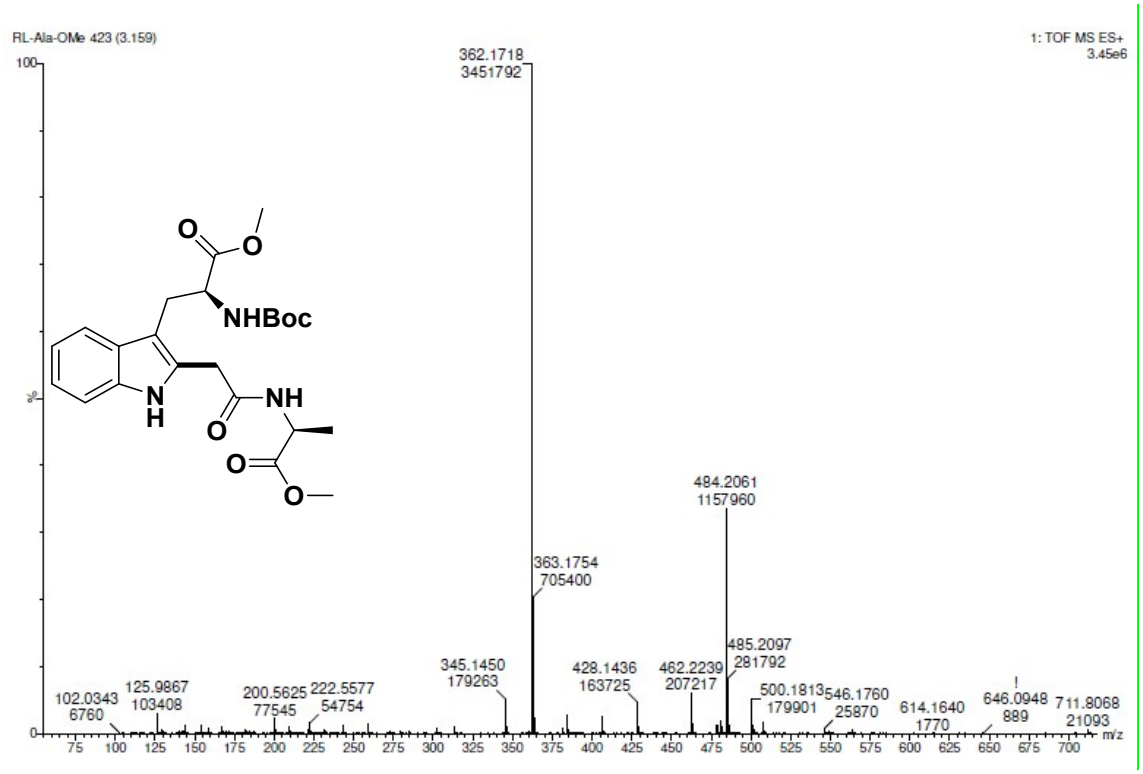


Figure S69. High Resolution Mass Spectra (HRMS) of **3k**

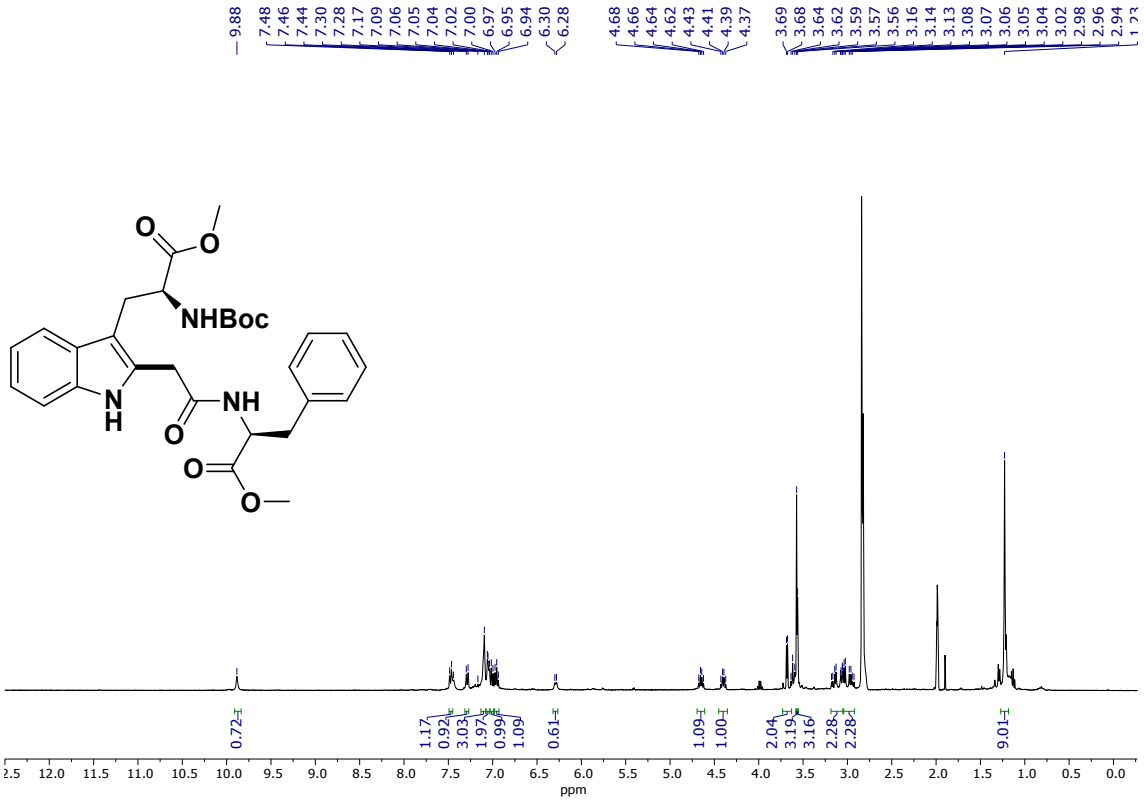


Figure S70. ^{1}H NMR (400 MHz, Acetone) of **3l**

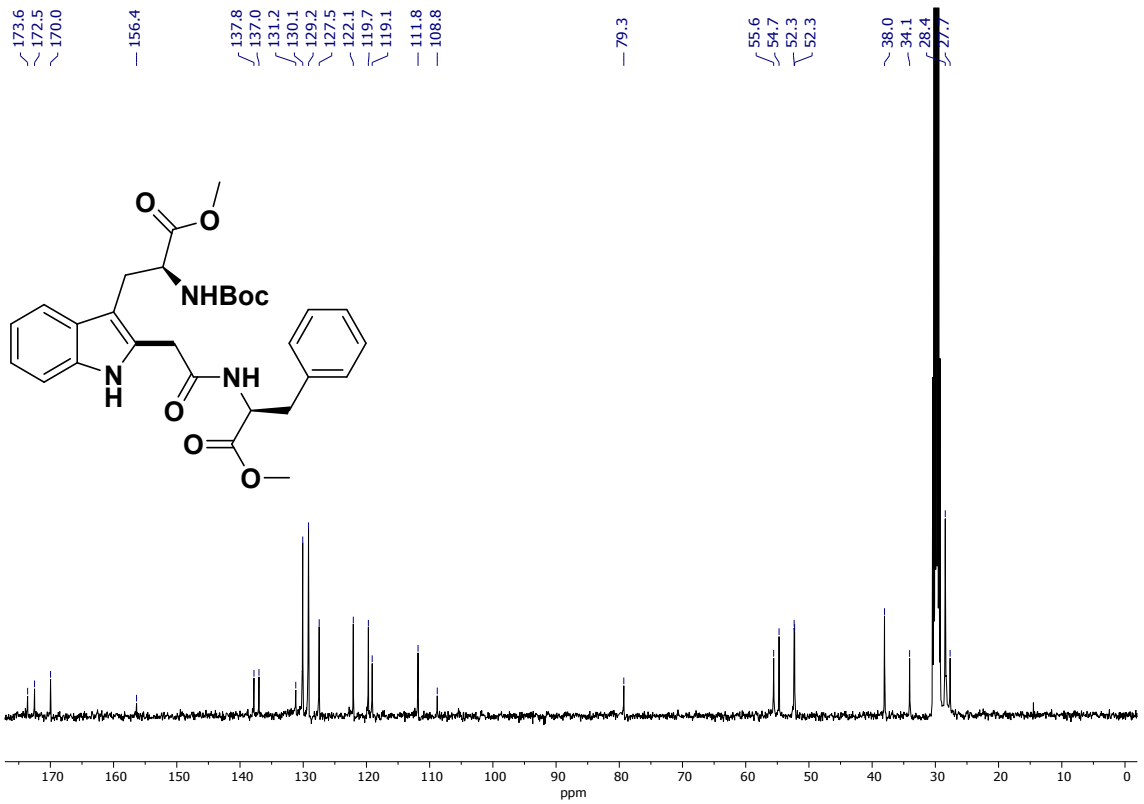


Figure S71. ^{13}C NMR (101 MHz, Acetone) of **3l**

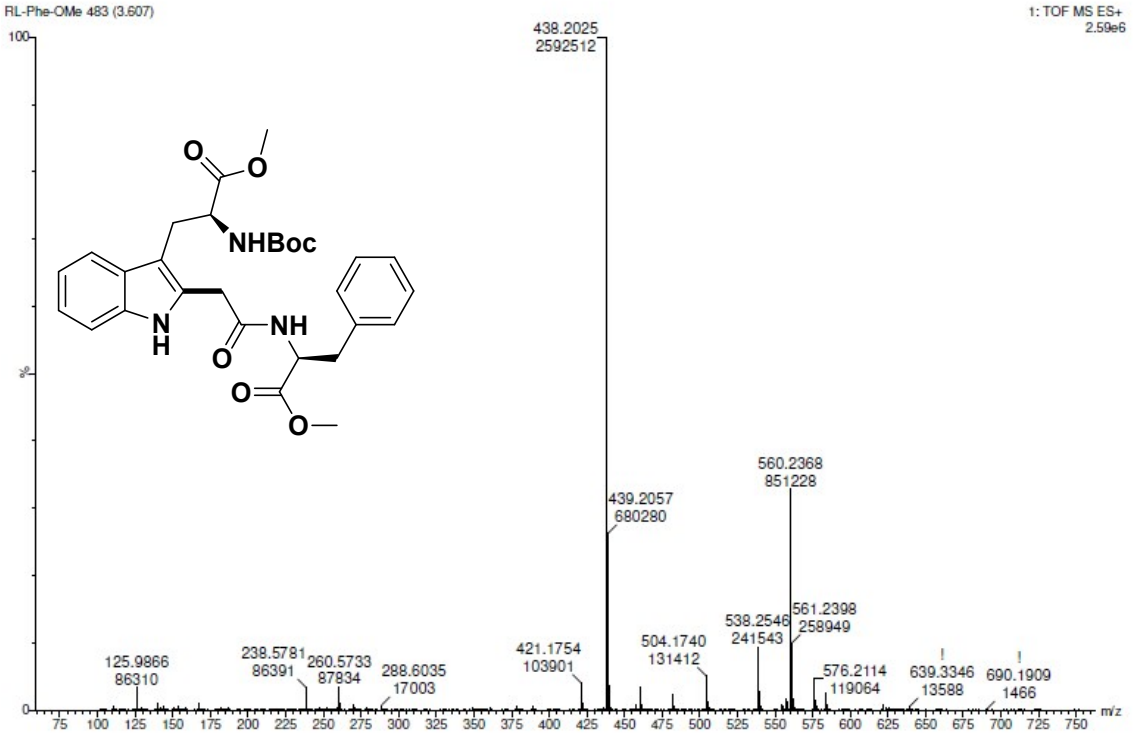


Figure S72. High Resolution Mass Spectra (HRMS) of **3l**

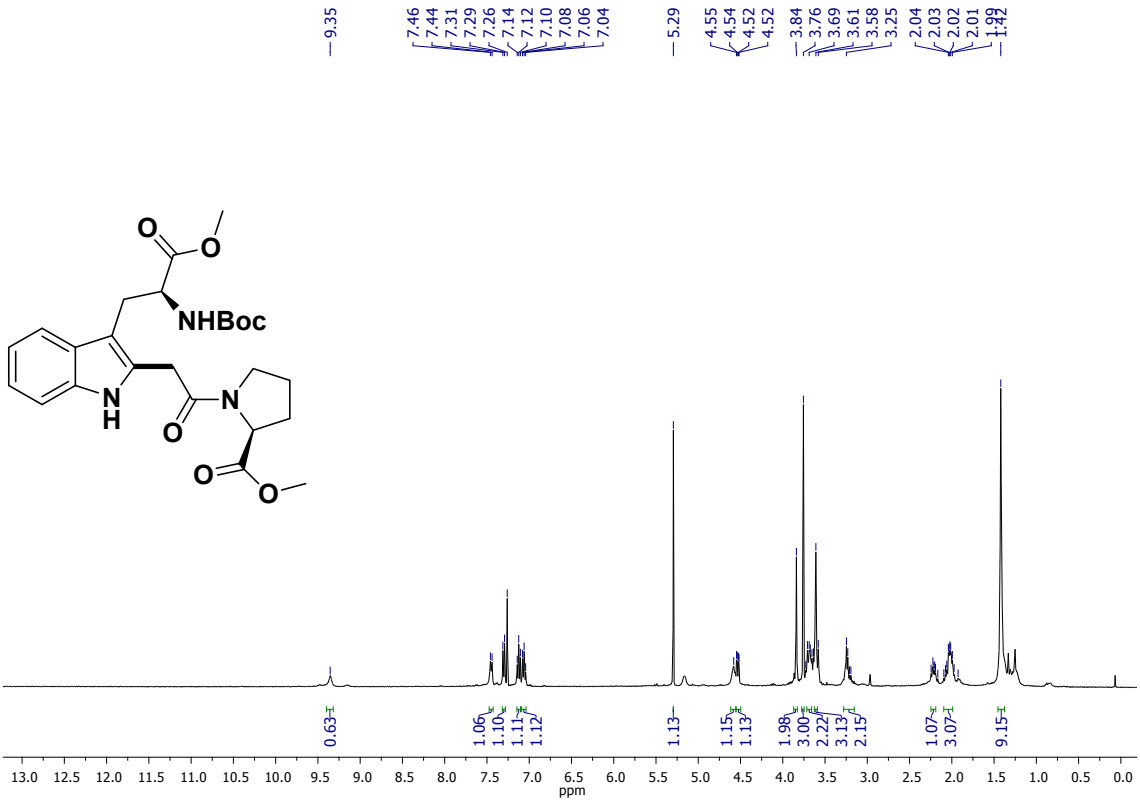


Figure S73. ^{1}H NMR (400 MHz, $CDCl_3$) of **3m**

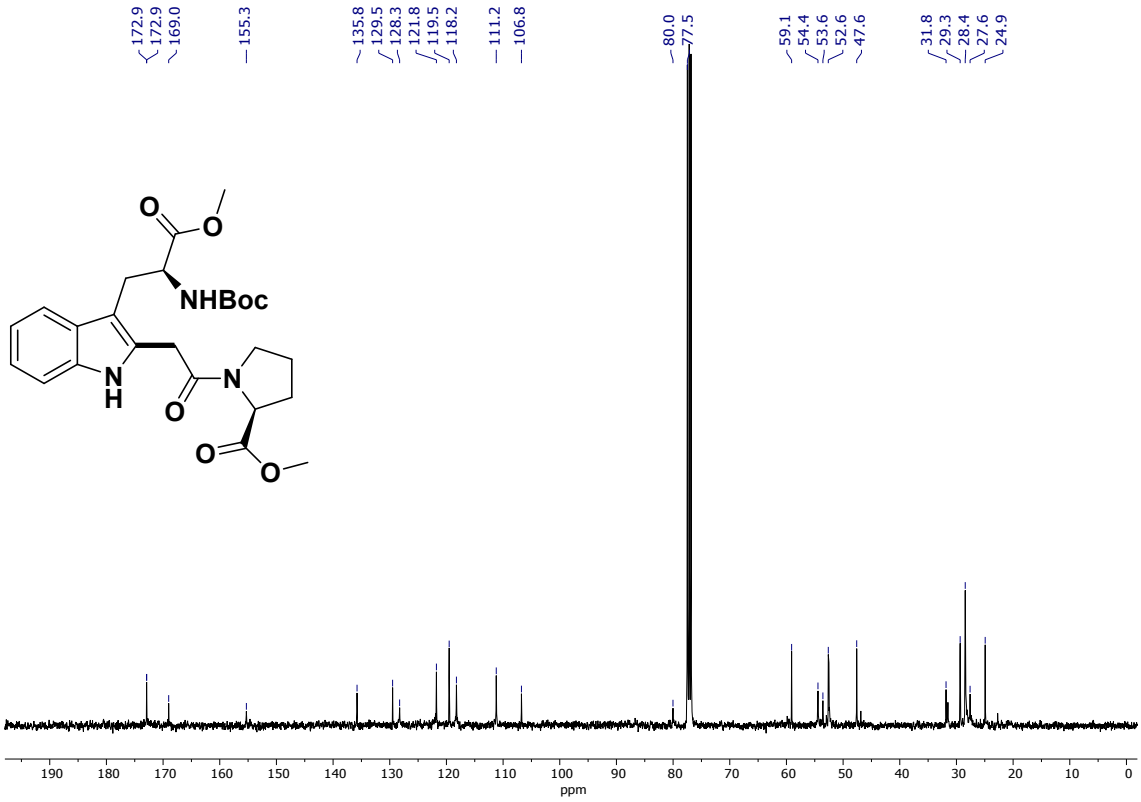


Figure S74. ^{13}C NMR (101 MHz, $CDCl_3$) of **3m**

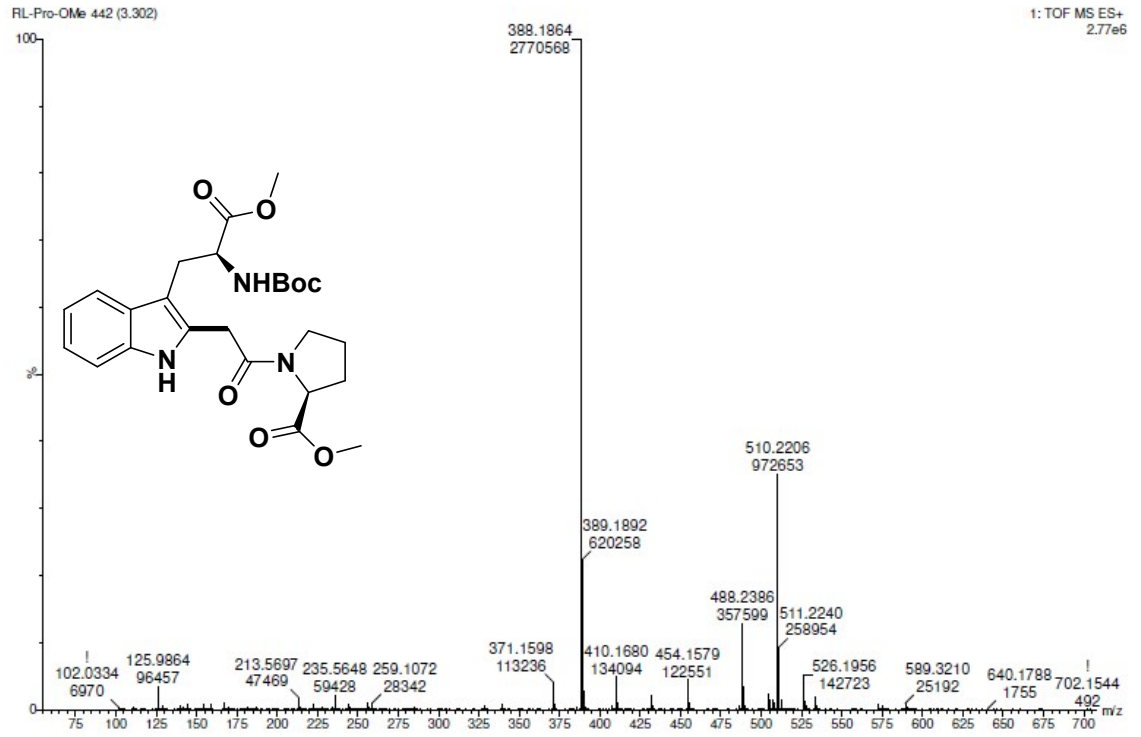


Figure S75. High Resolution Mas Spectra (HRMS) of **3m**

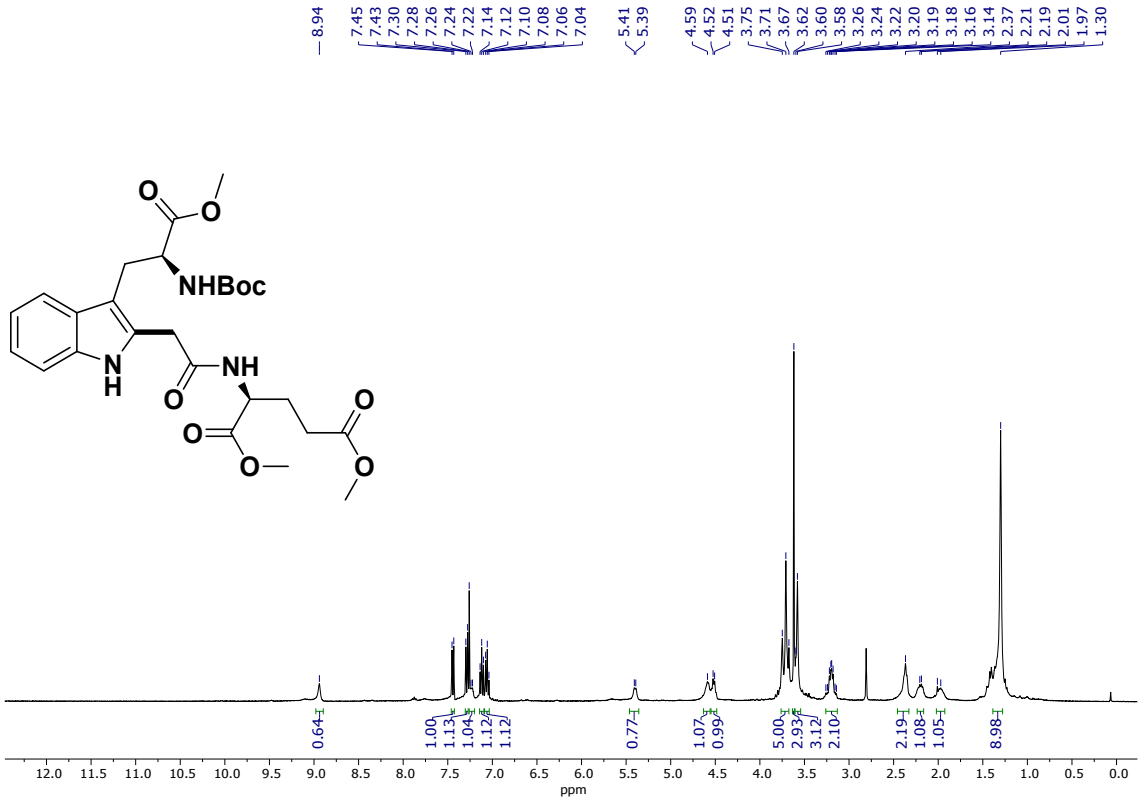


Figure S76. ^{1}H NMR (400 MHz, $CDCl_3$) of **3n**

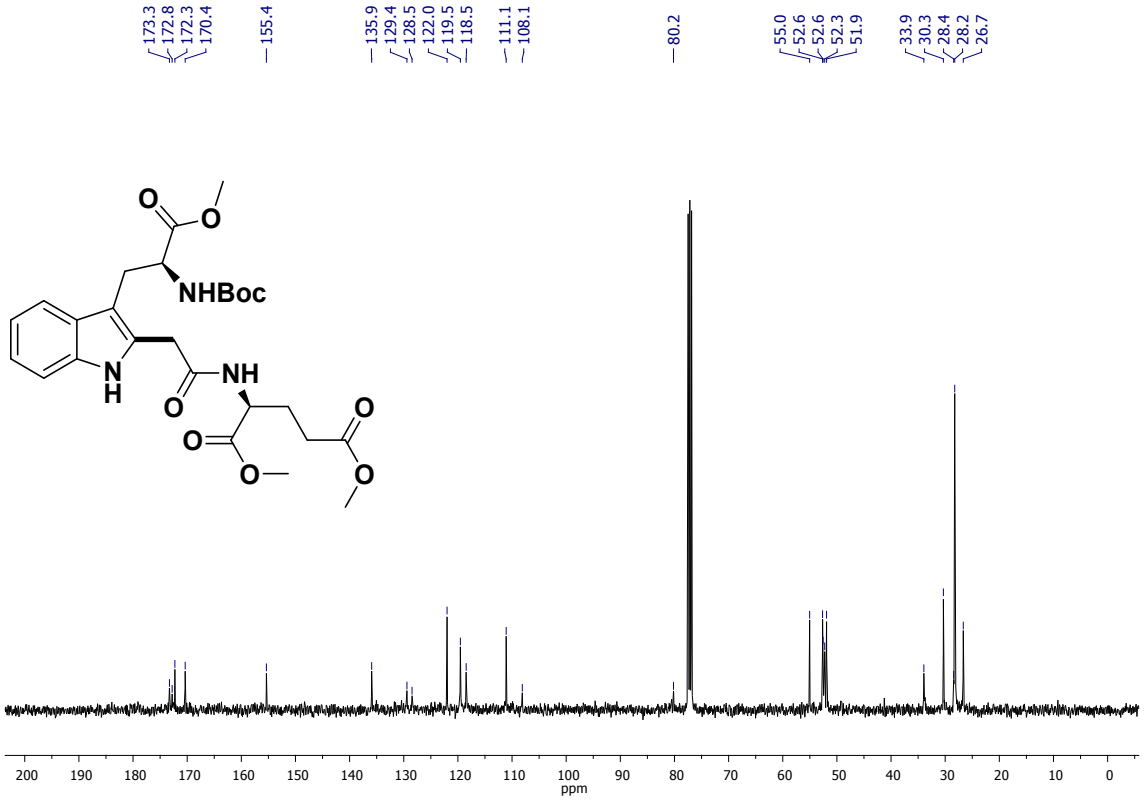


Figure S77. ^{13}C NMR (101 MHz, $CDCl_3$) of **3n**

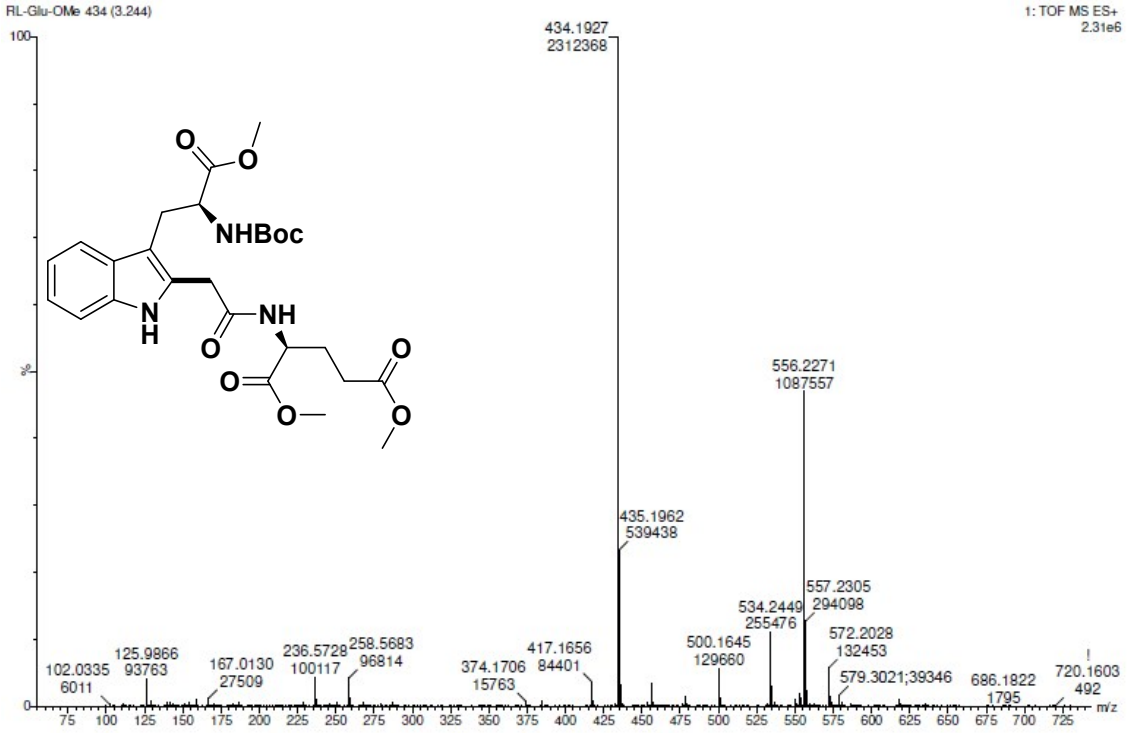


Figure S78. High Resolution Mass Spectra (HRMS) of **3n**

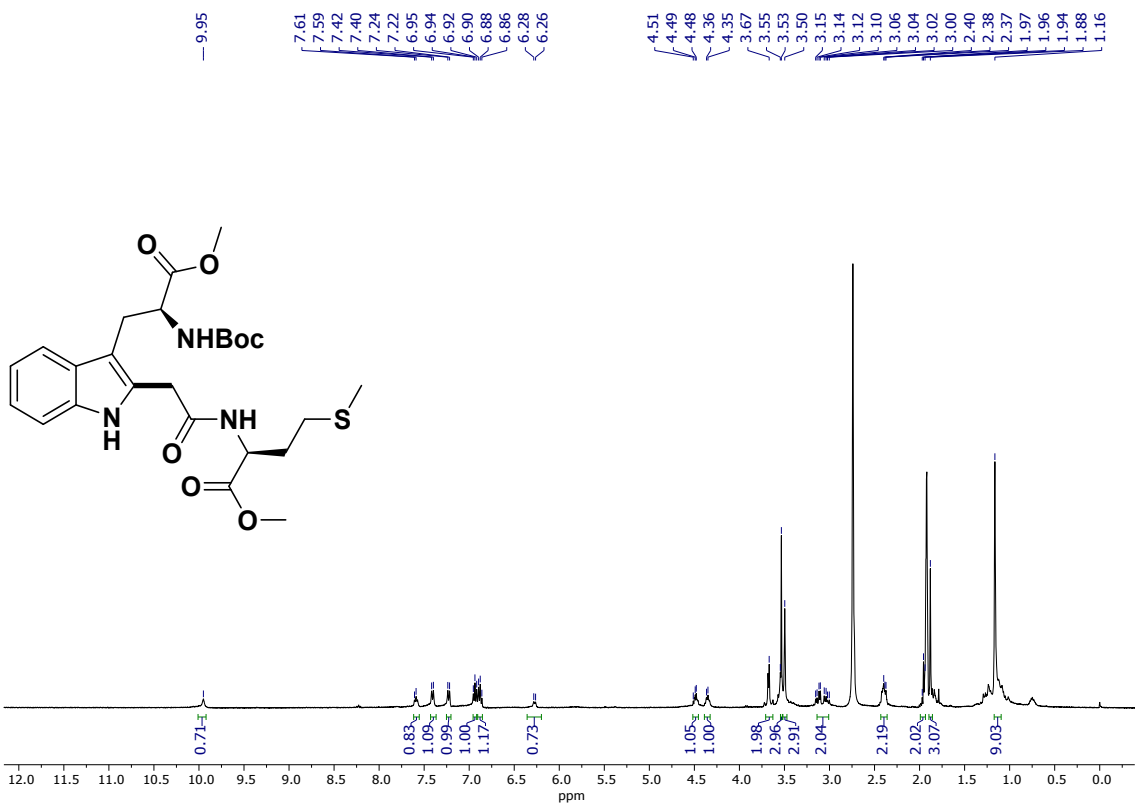


Figure S79. ^{1}H NMR (400 MHz, Acetone) of **3o**

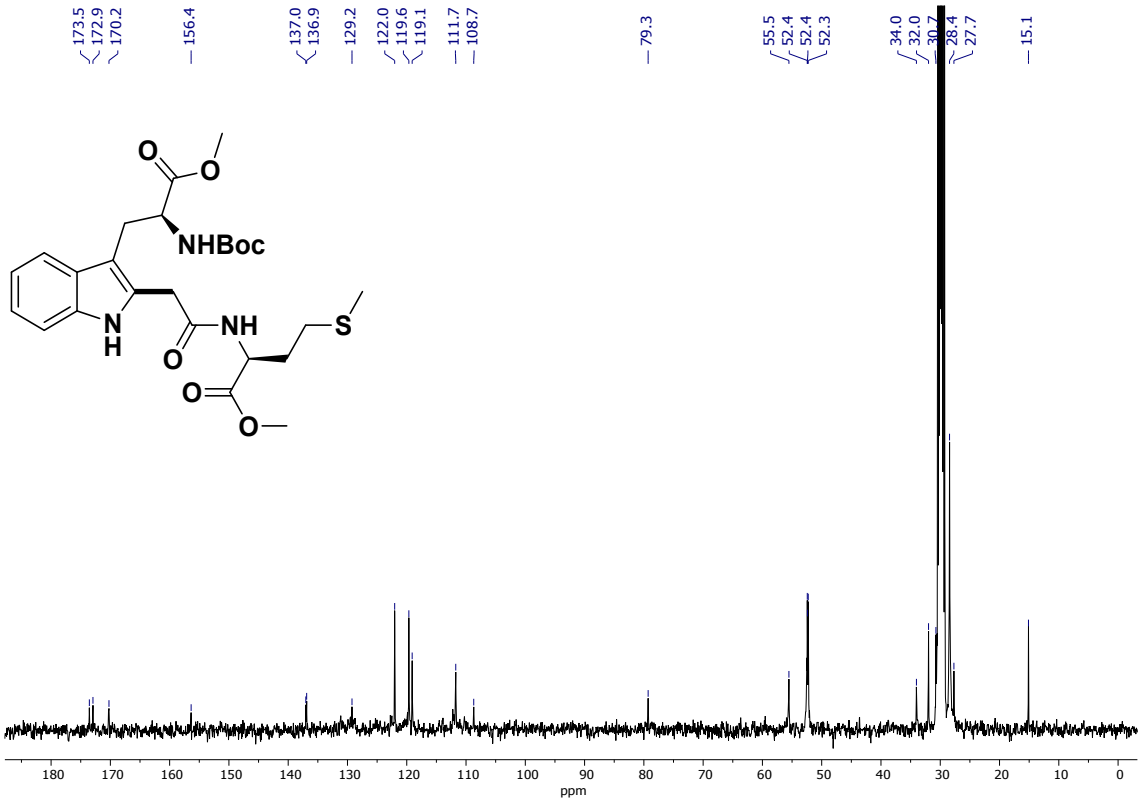


Figure S80. ^{13}C NMR (101 MHz, Acetone) of **3o**

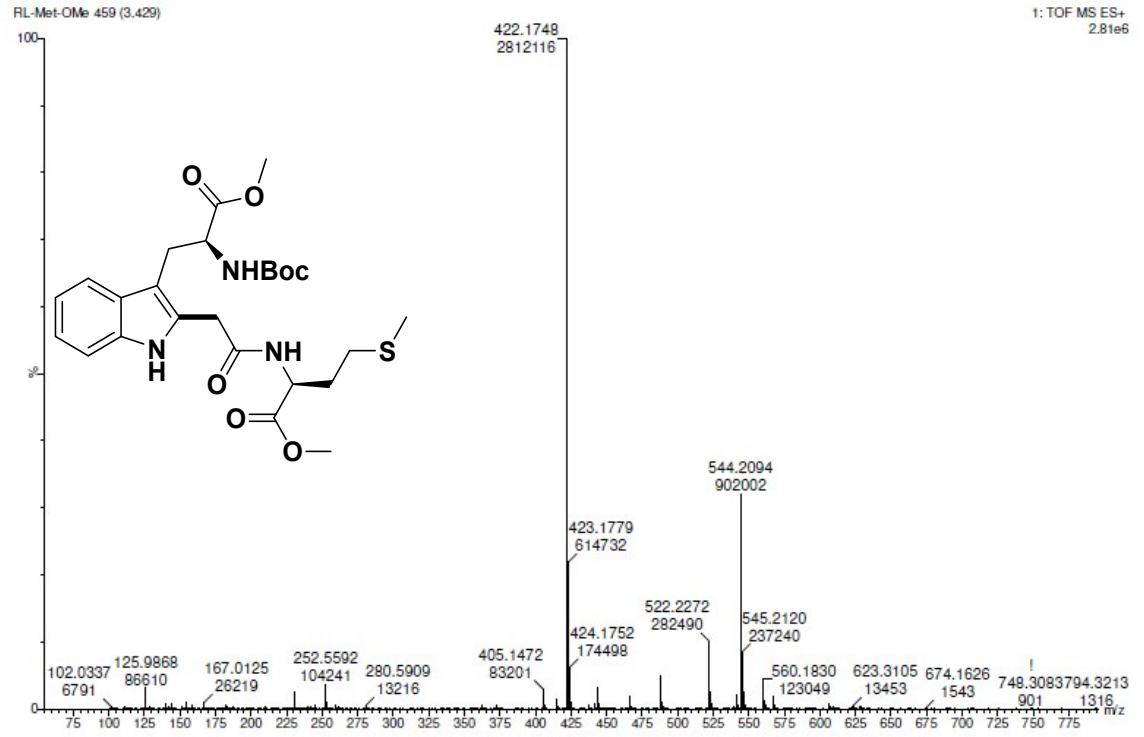


Figure S81. High Resolution Mass Spectra (HRMS) of **3o**

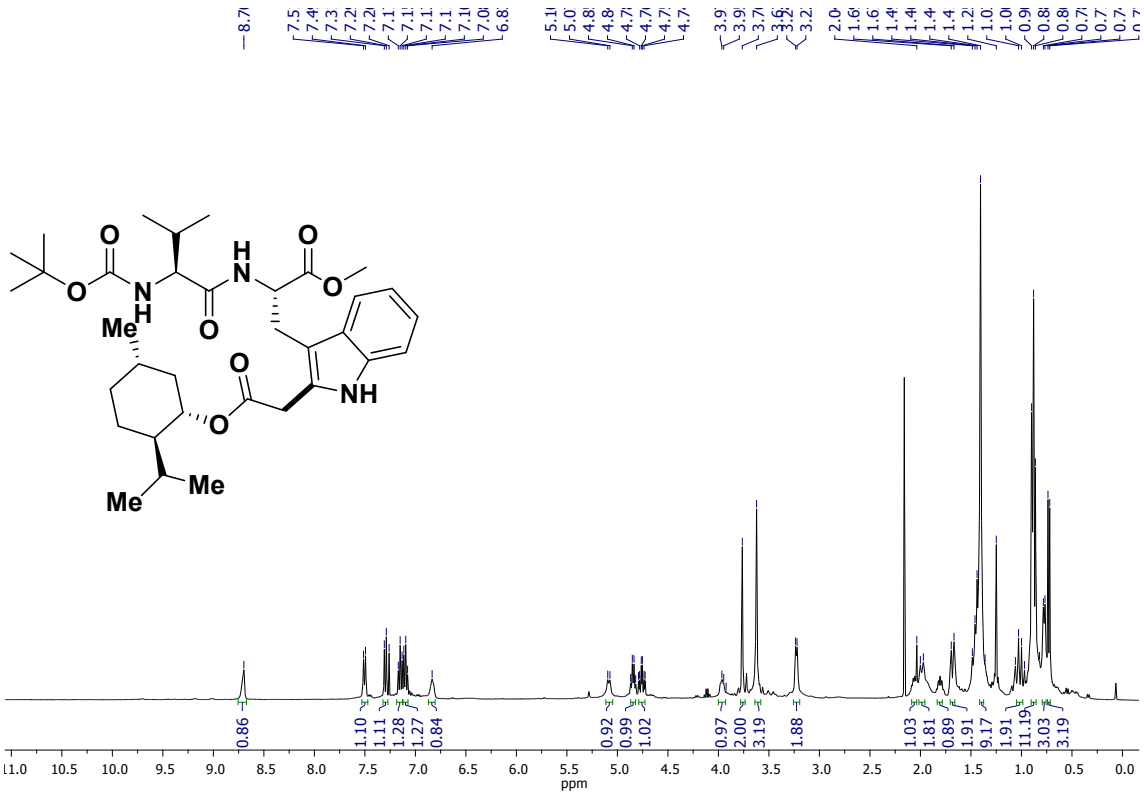


Figure S82. ^{1}H NMR (400 MHz, $CDCl_3$) of **4b**

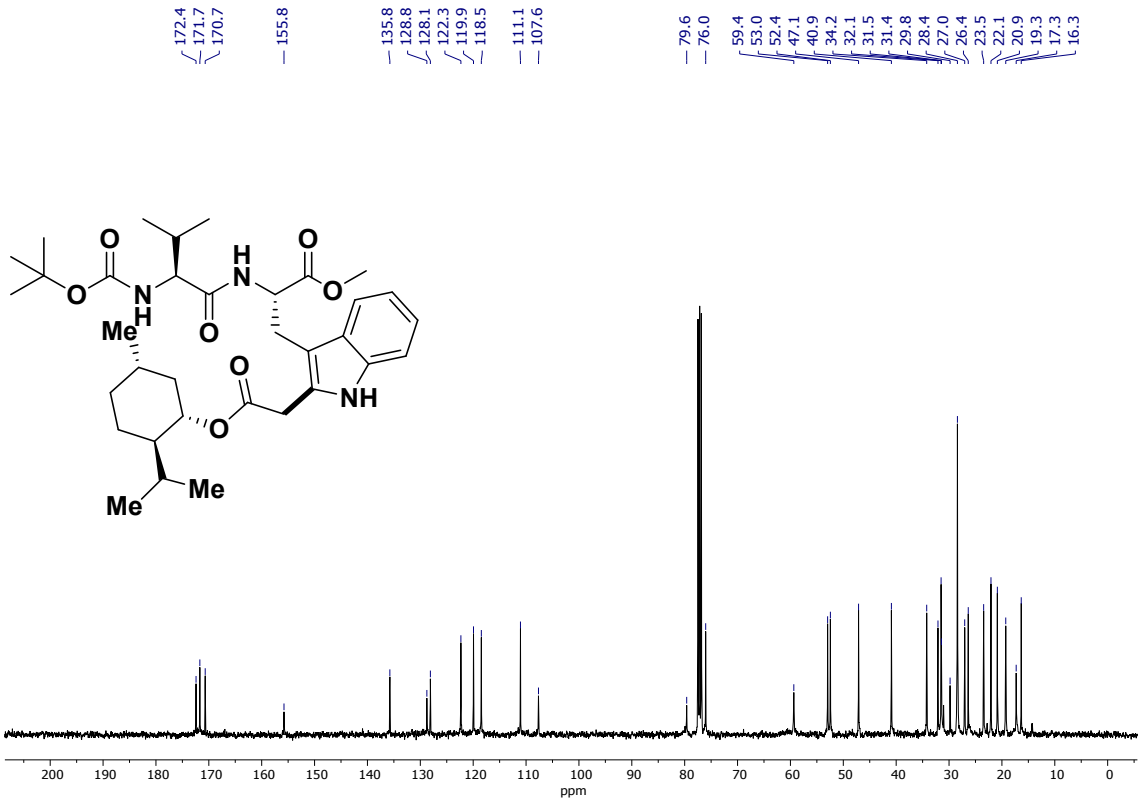


Figure S83. ^{13}C NMR (101 MHz, $CDCl_3$) of **4b**

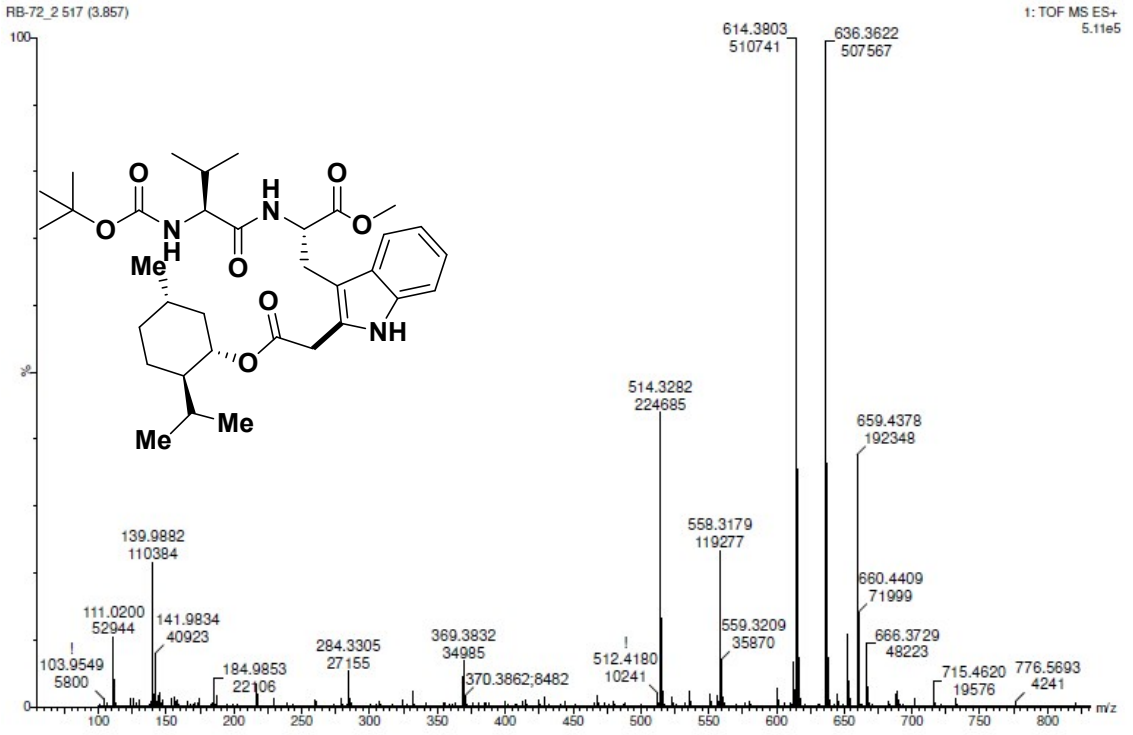


Figure S84. High Resolution Mass Spectra (HRMS) of **4b**

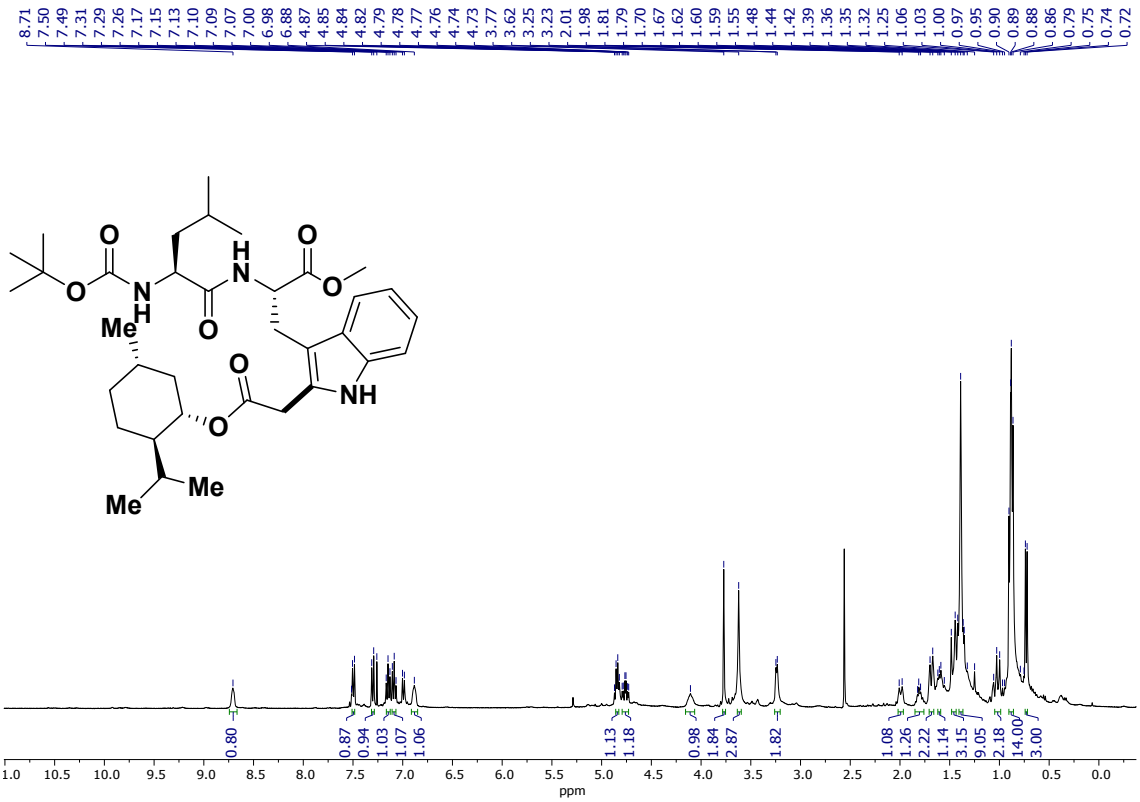


Figure S85. ^{1}H NMR (400 MHz, $CDCl_3$) of **4c**

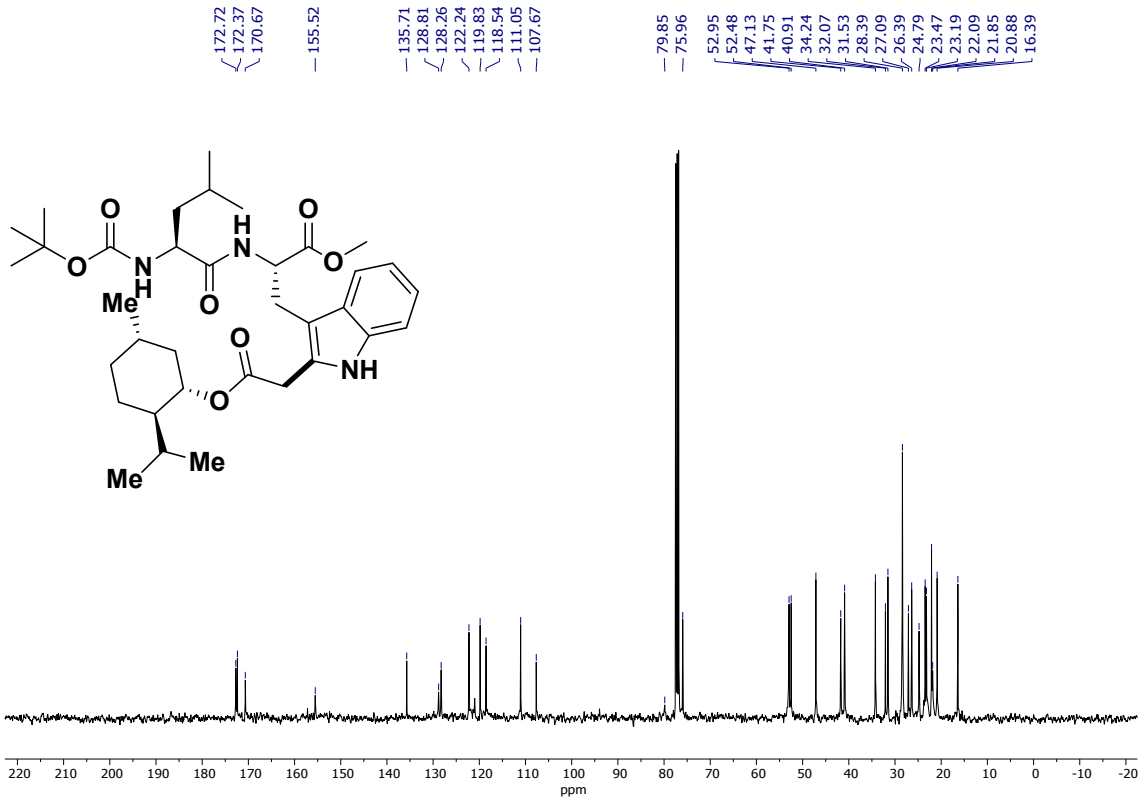


Figure S86.^{13}C NMR (101 MHz, $CDCl_3$) of **4c**

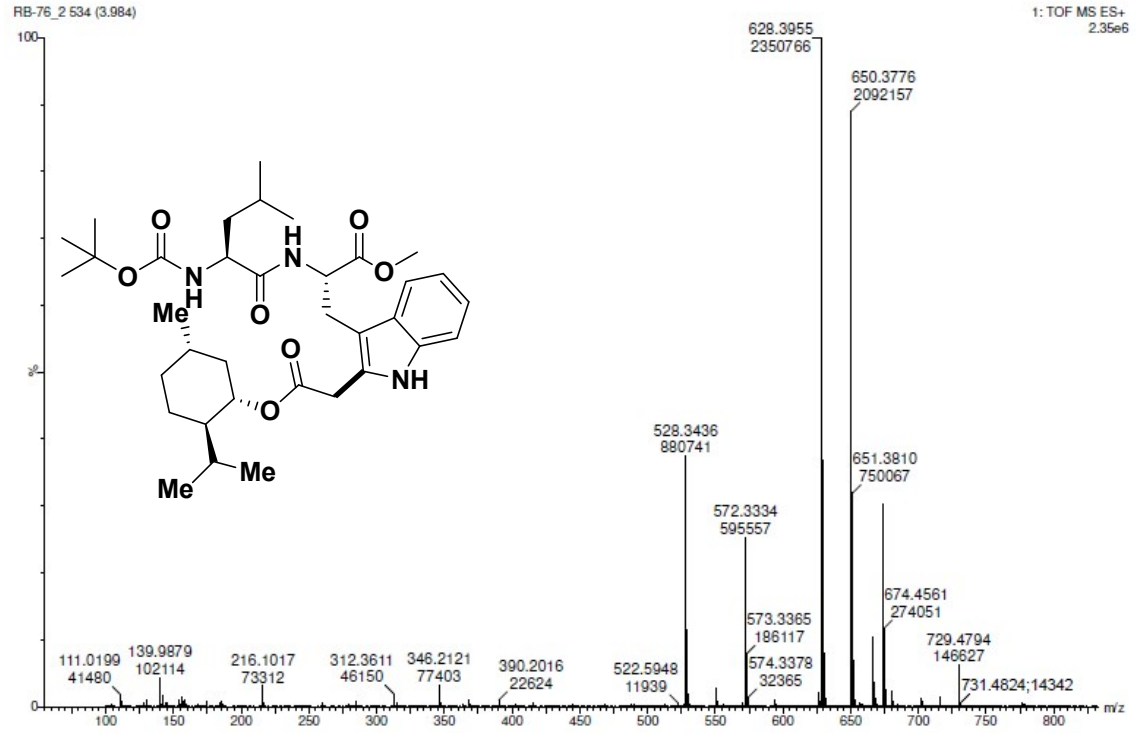


Figure S87. High Resolution Mass Spectra (HRMS) of **4c**

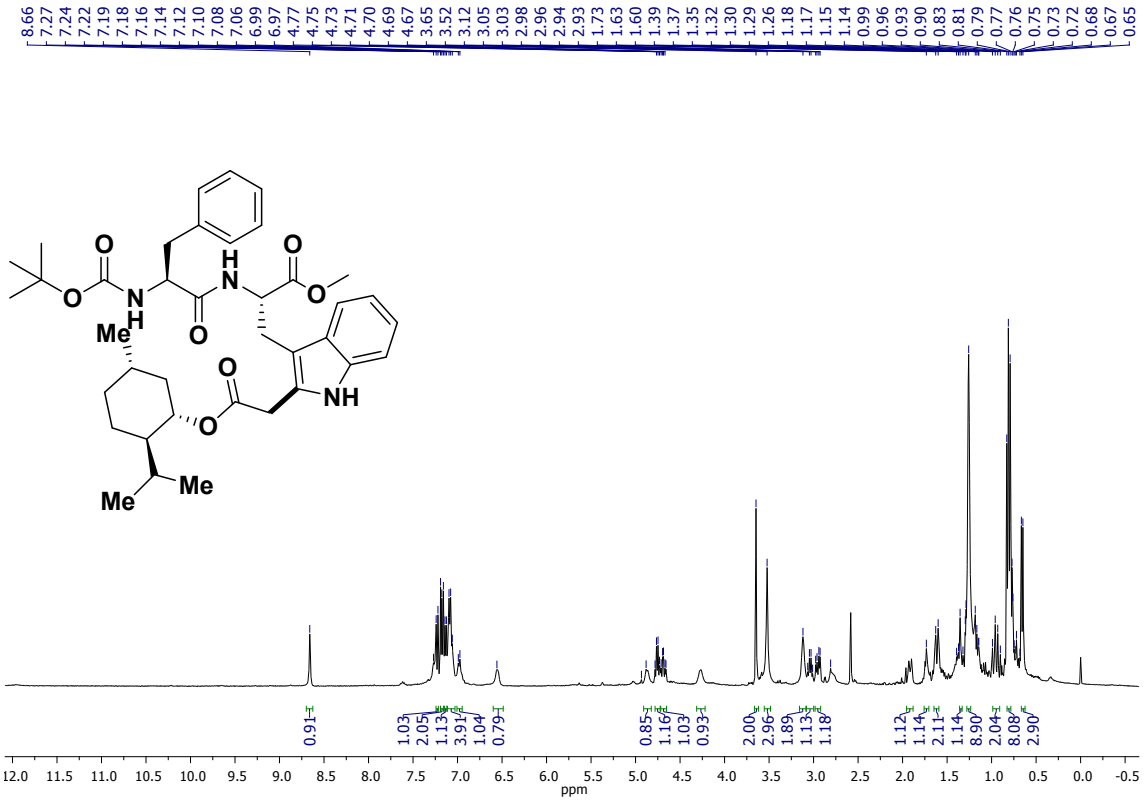


Figure S88. ^{1}H NMR (400 MHz, $CDCl_3$) of **4d**

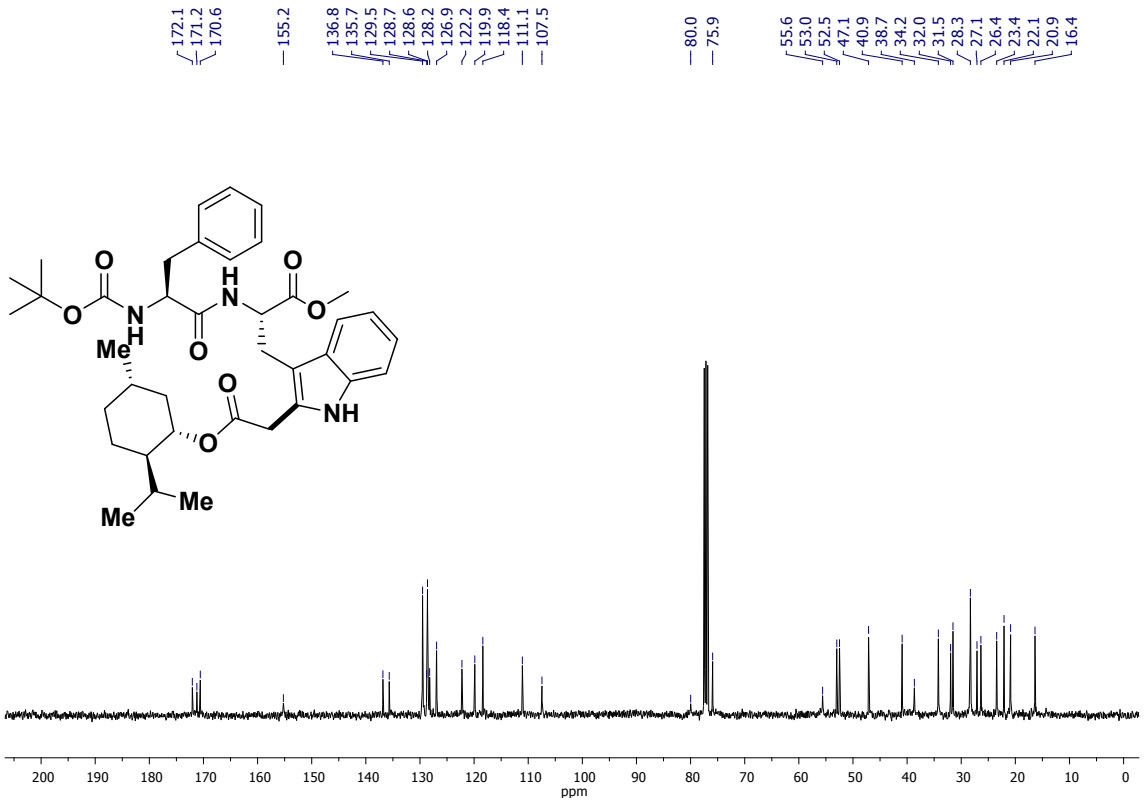


Figure S89. ^{13}C NMR (101 MHz, $CDCl_3$) of **4d**

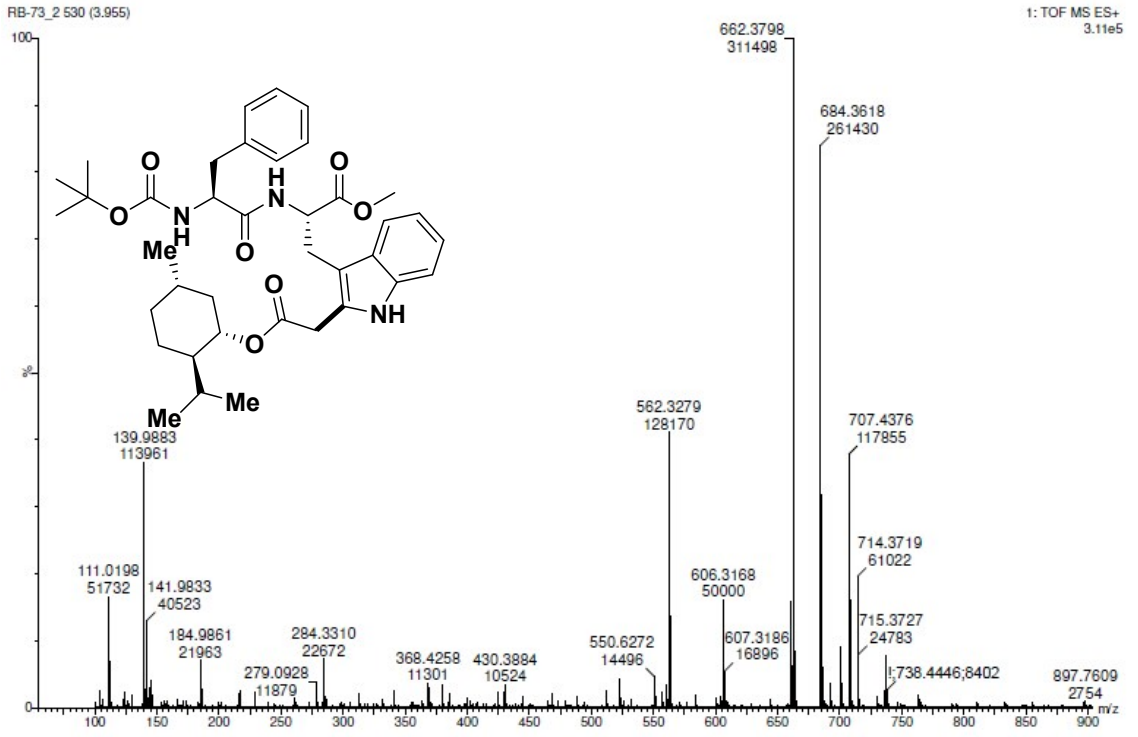


Figure S90. High Resolution Mass Spectra of **4d**

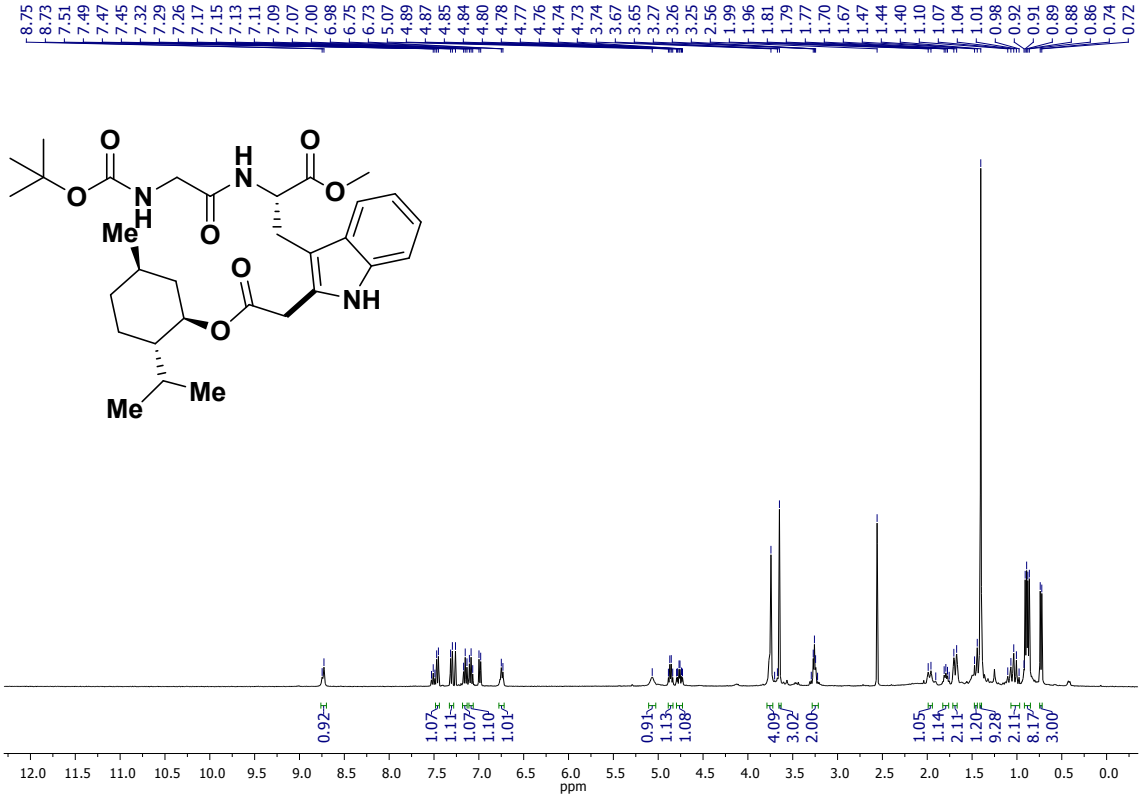


Figure S91.[1]H NMR (400 MHz, $CDCl_3$) of **4e**

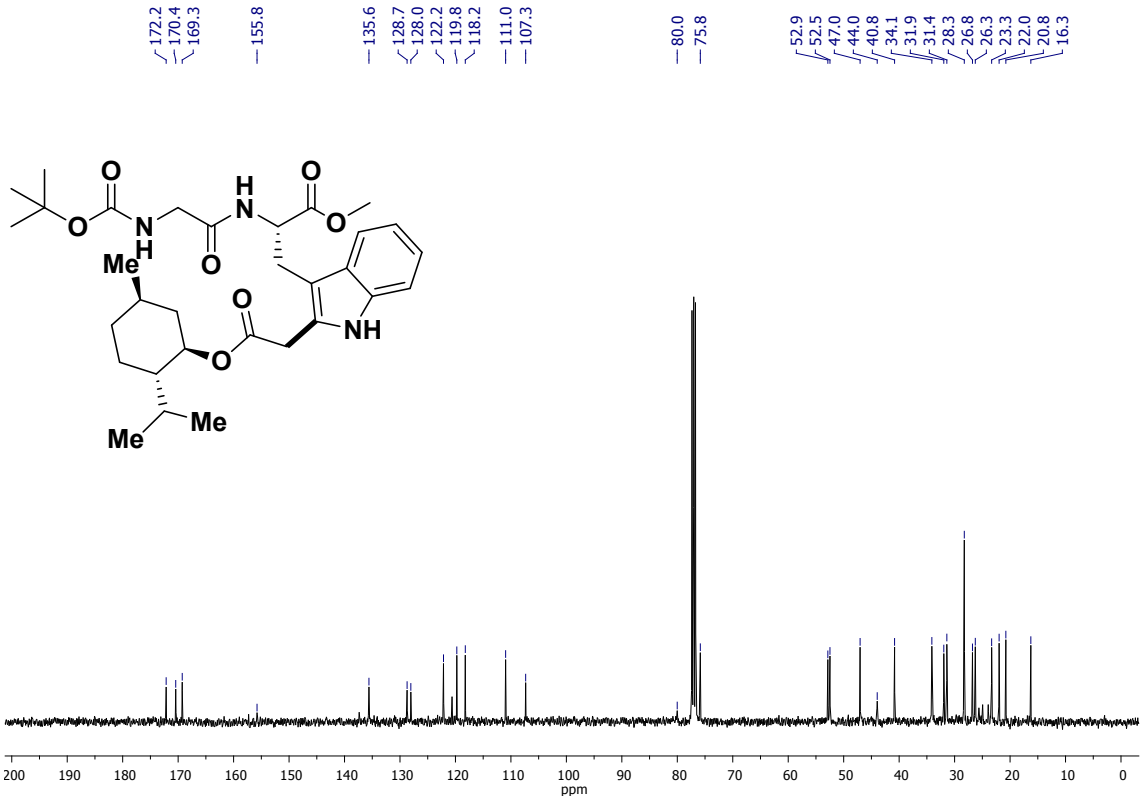


Figure S92.^{13}C NMR (101 MHz, $CDCl_3$) of **4e**

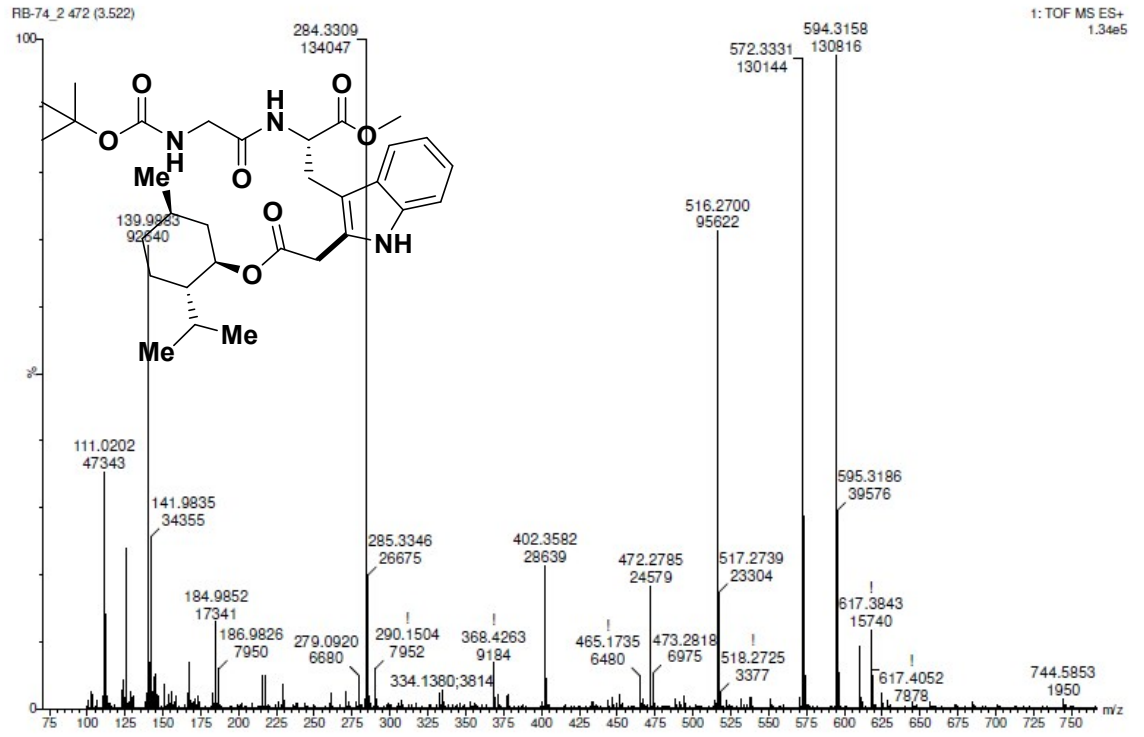


Figure S93. High Resolution Mass Spectra (HRMS) of **4e**

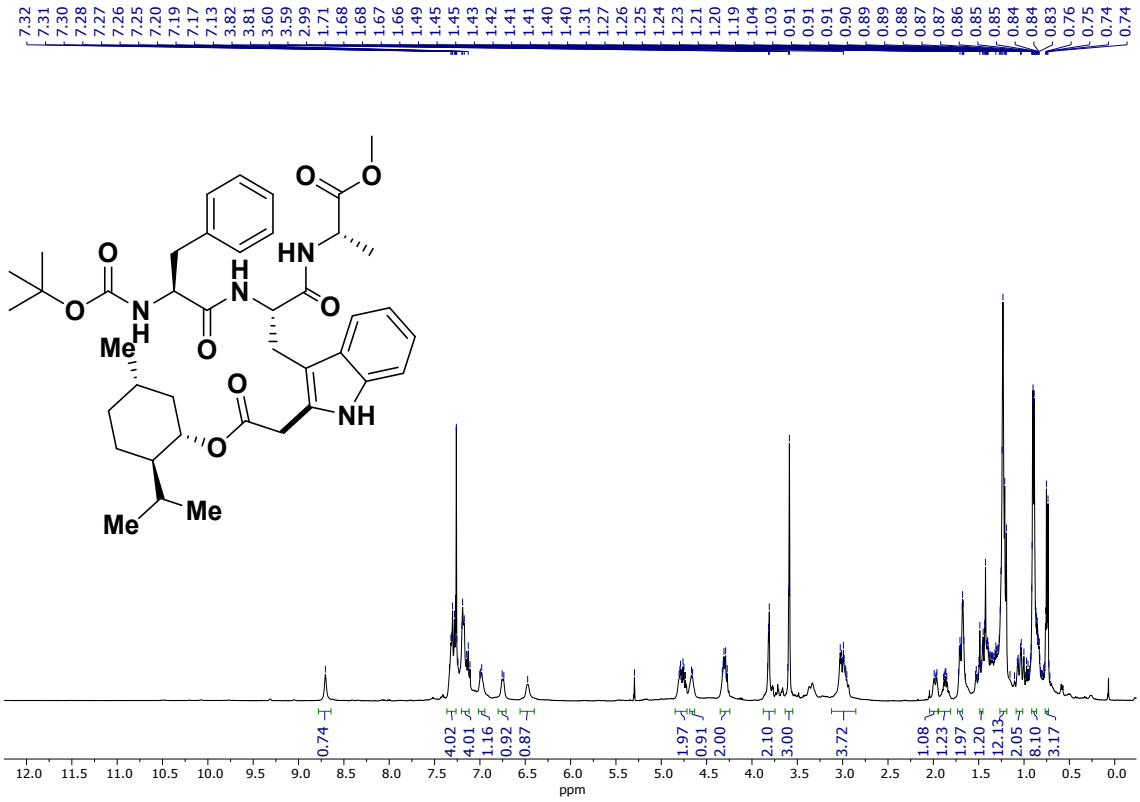


Figure S94.[1]H NMR (400 MHz, $CDCl_3$) of **4f**

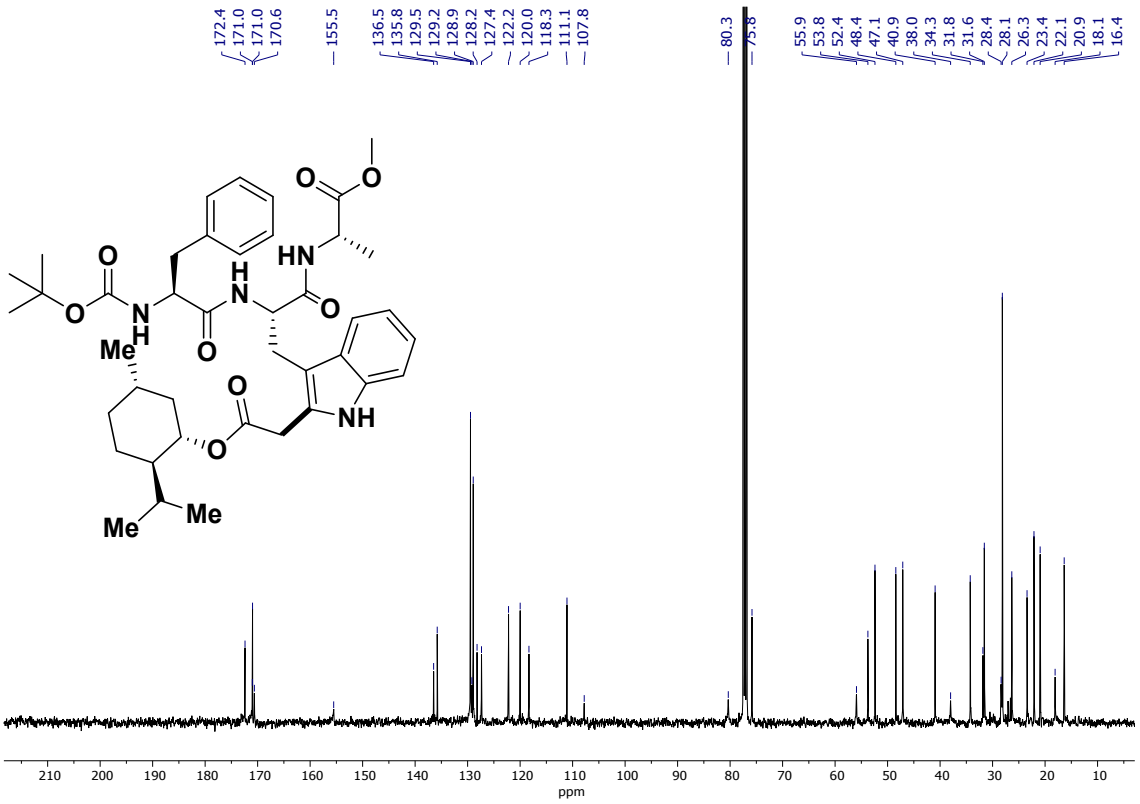


Figure S95.[13]C NMR (101 MHz, $CDCl_3$) of **4f**

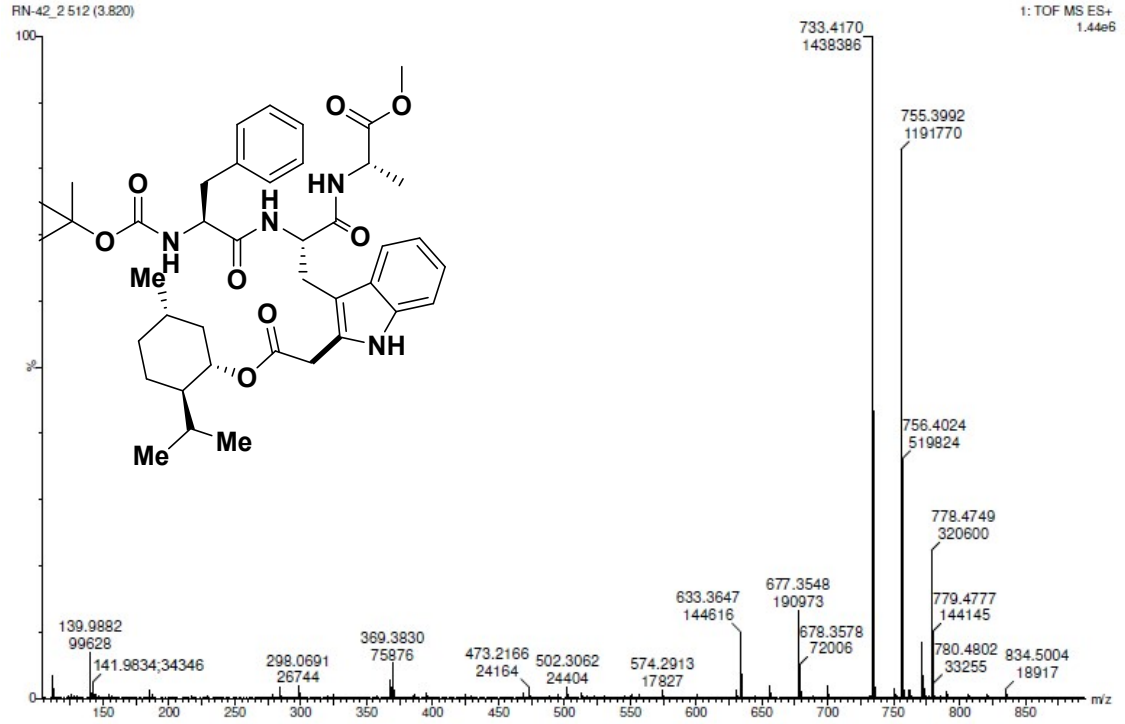


Figure S96. High Resolution Mass Spectra (HRMS) of **4f**

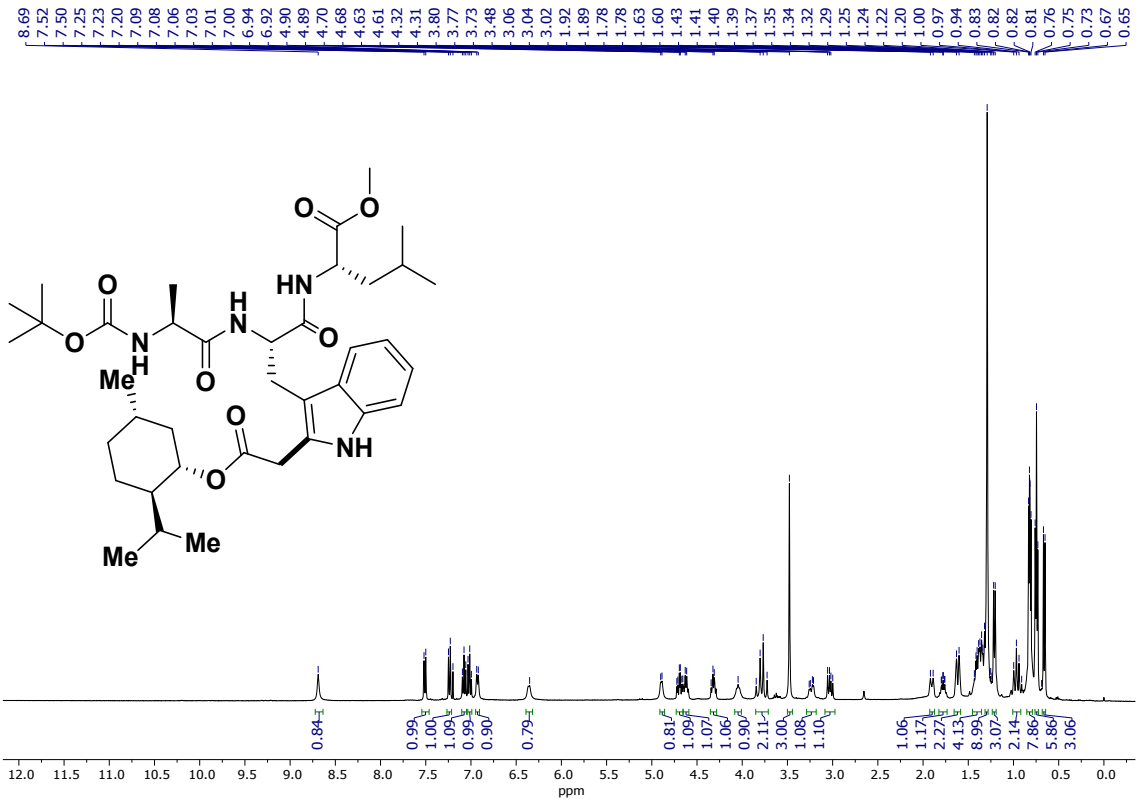


Figure S97. ^{1}H NMR (400 MHz, $CDCl_3$) of **4g**

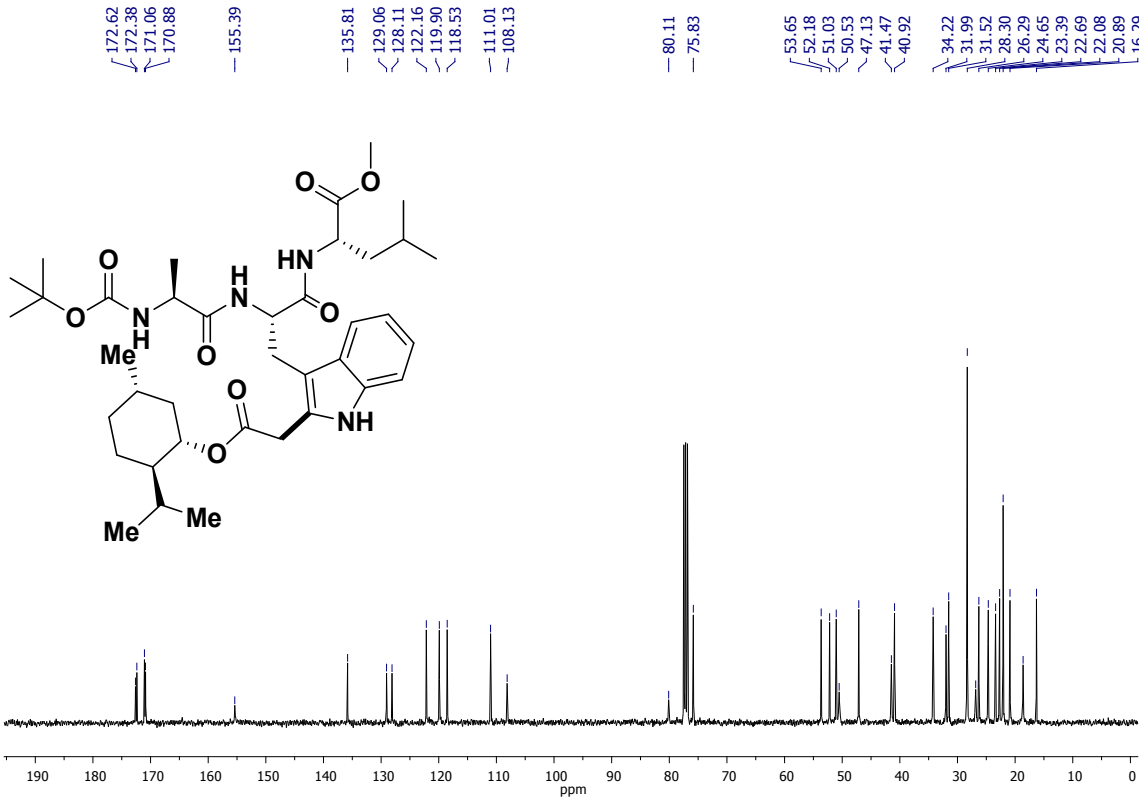


Figure S98. ^{13}C NMR (101 MHz, $CDCl_3$) of **4g**

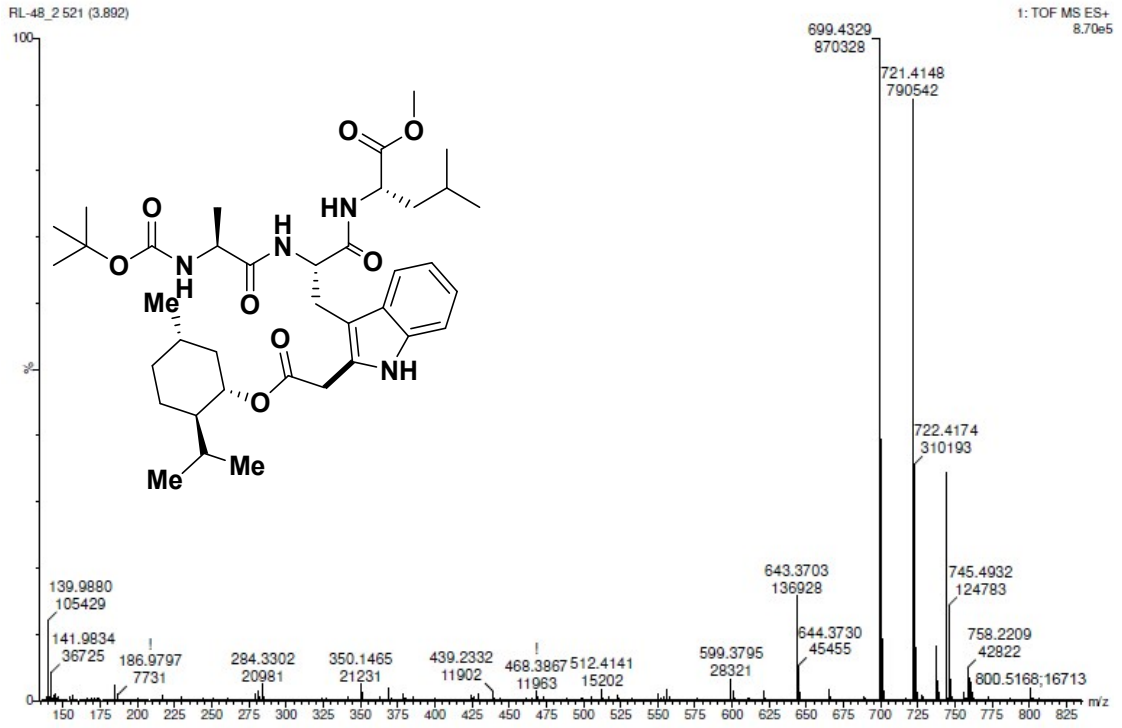


Figure S99. High Resolution Mass Spectra (HRMS) of **4g**

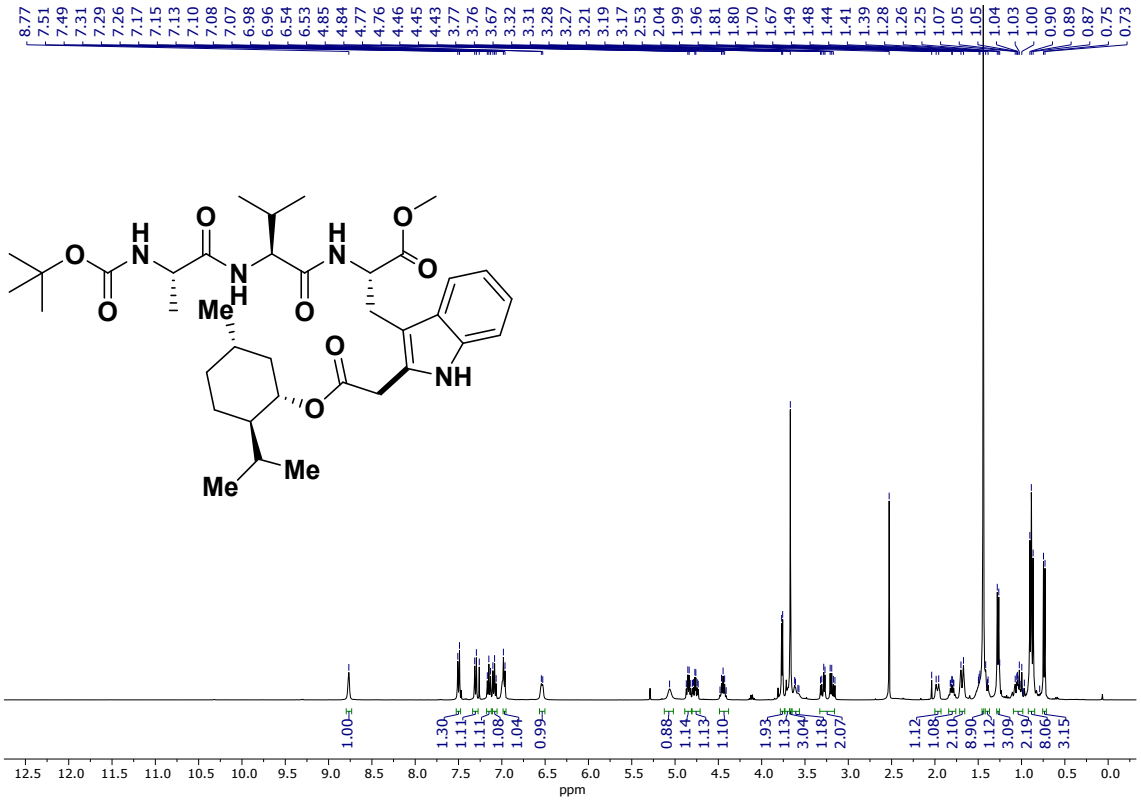


Figure S100. ^{1}H NMR (400 MHz, $CDCl_3$) of **4h**

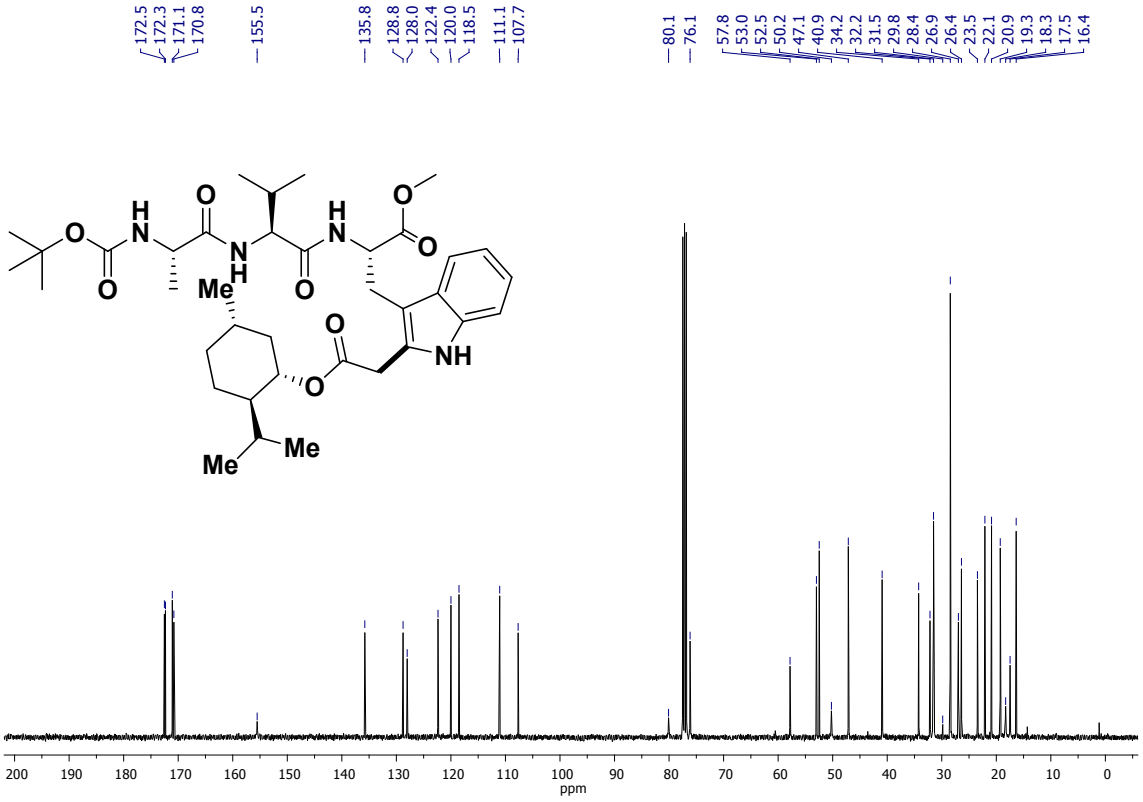


Figure S101. ^{13}C NMR (101 MHz, $CDCl_3$) of **4h**

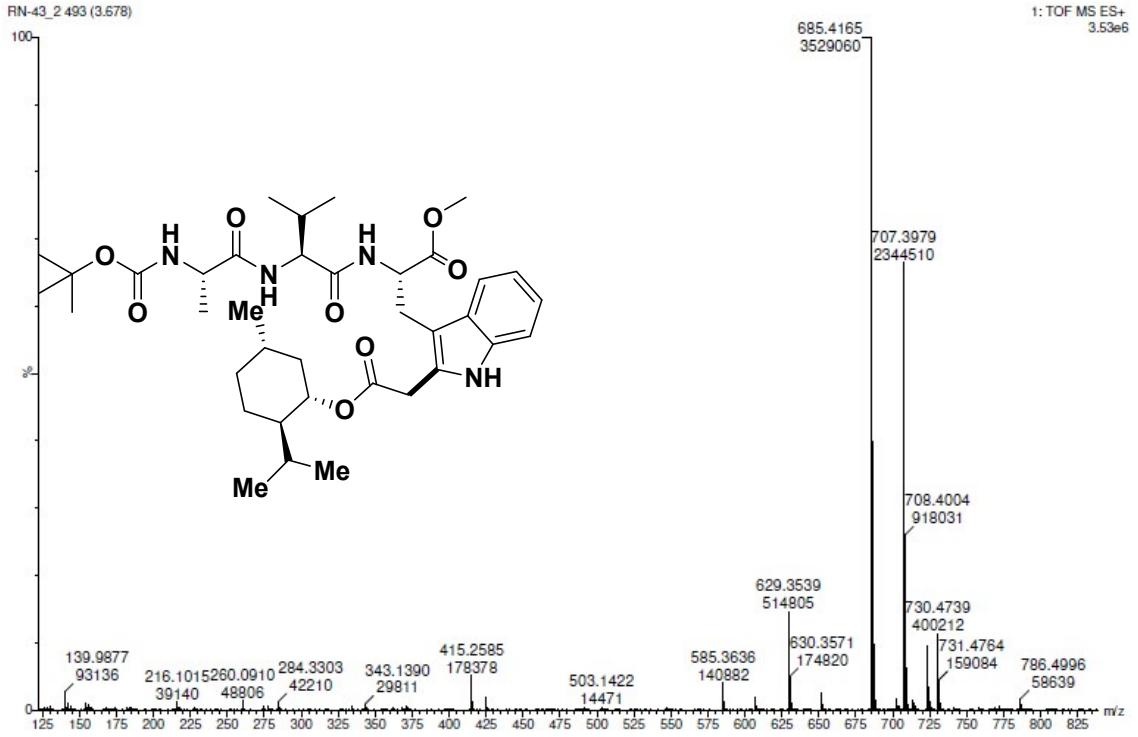


Figure S102. High Resolution Mass Spectra (HRMS) of **4h**

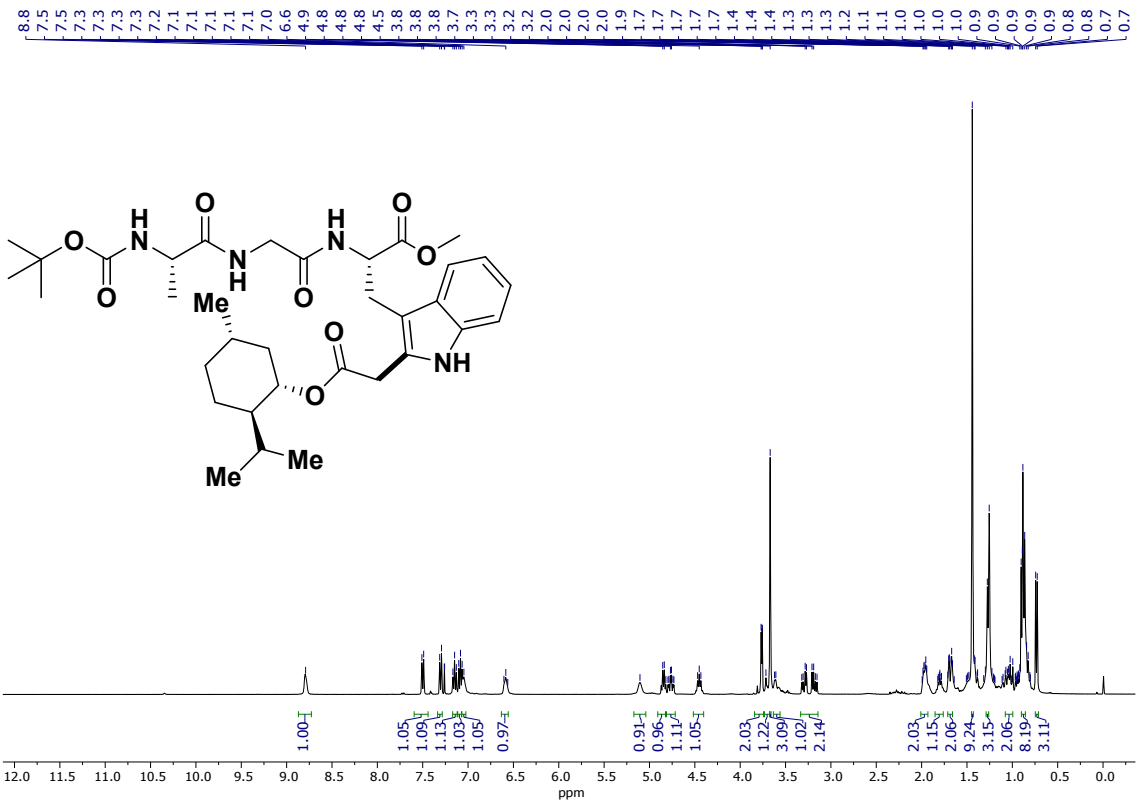


Figure S103. ^{1}H NMR (400 MHz, $CDCl_3$) of **4i**

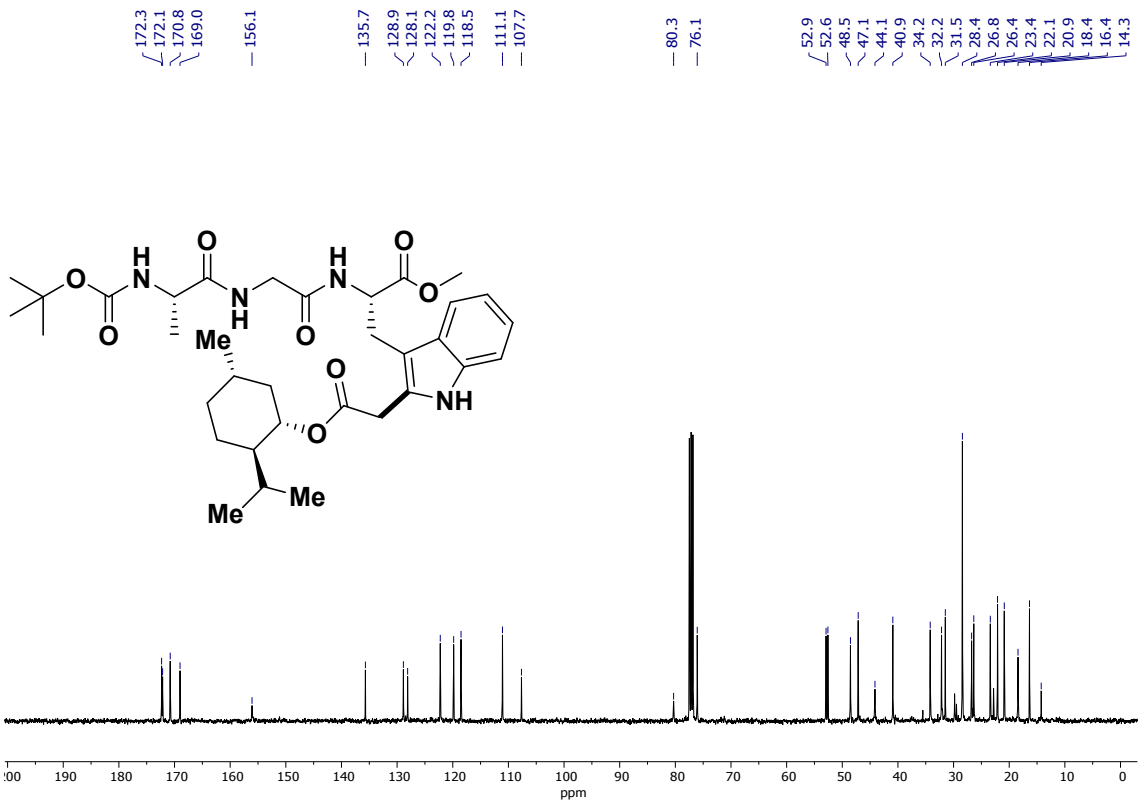


Figure S104. ^{13}C NMR (101 MHz, $CDCl_3$) of **4i**

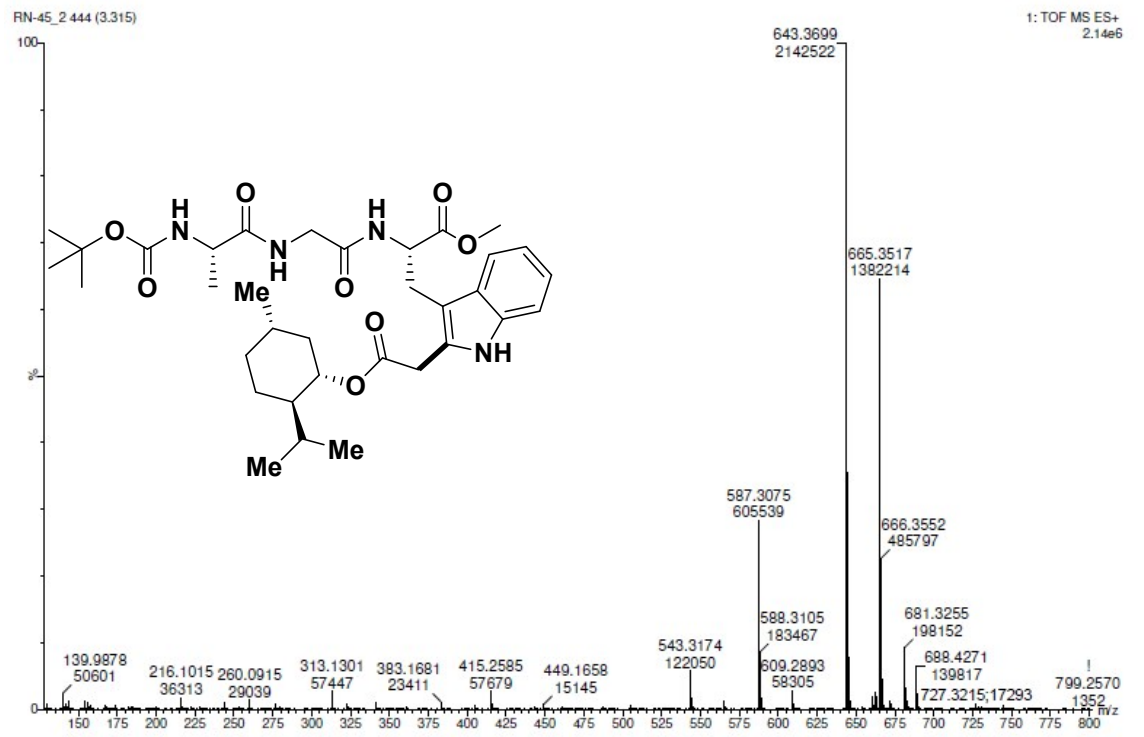


Figure S105. High Resolution Mass Spectra (HRMS) of **4i**

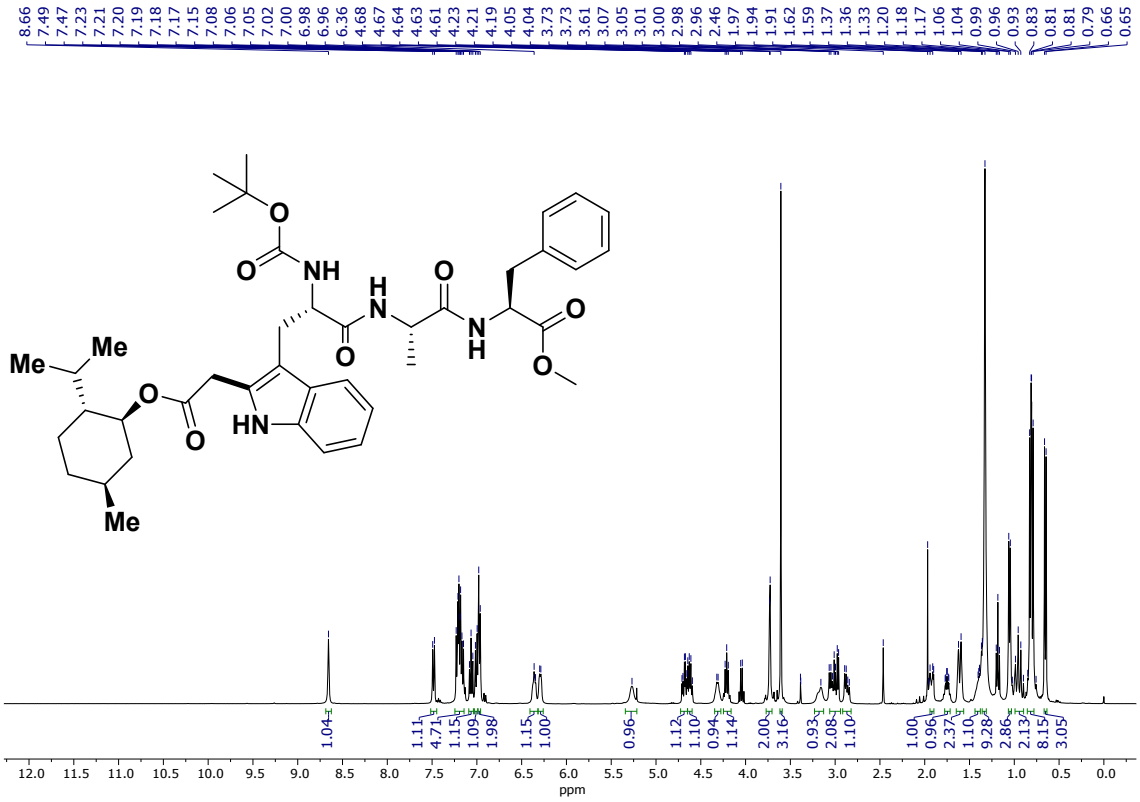


Figure S106. ^{1}H NMR (400 MHz, $CDCl_3$) of **4j**

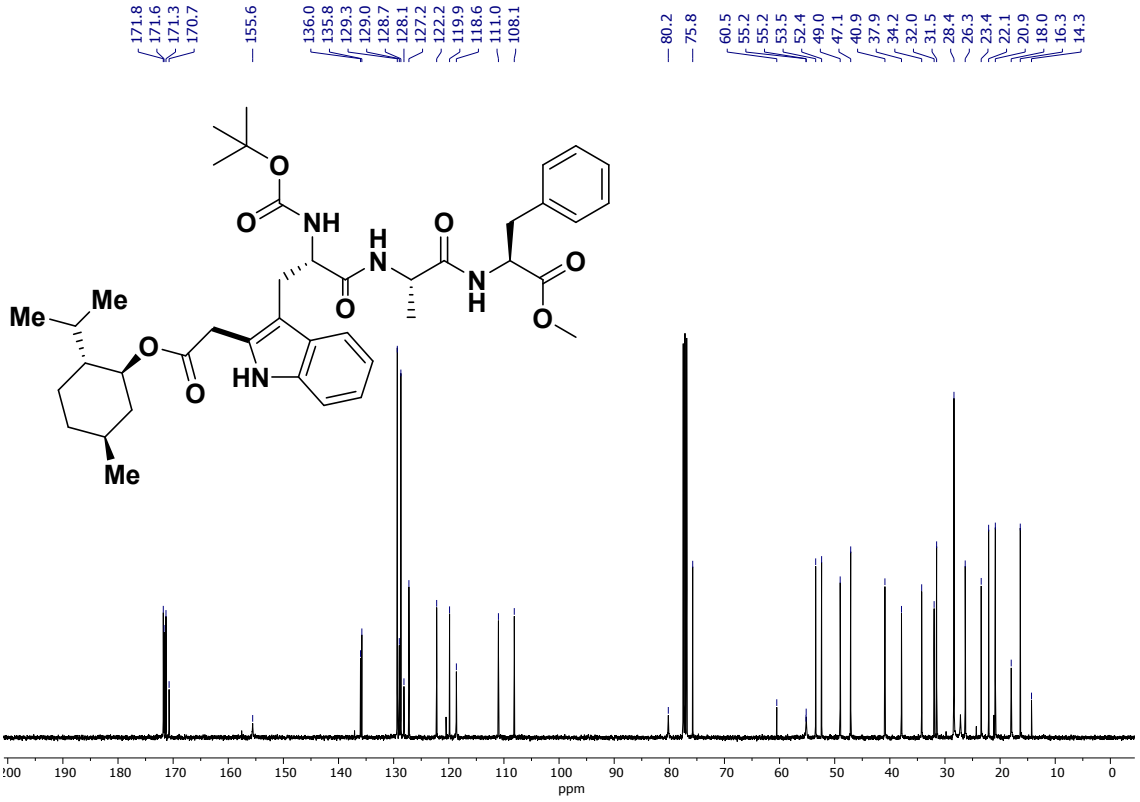


Figure S107. ^{13}C NMR (101 MHz, $CDCl_3$) of **4j**

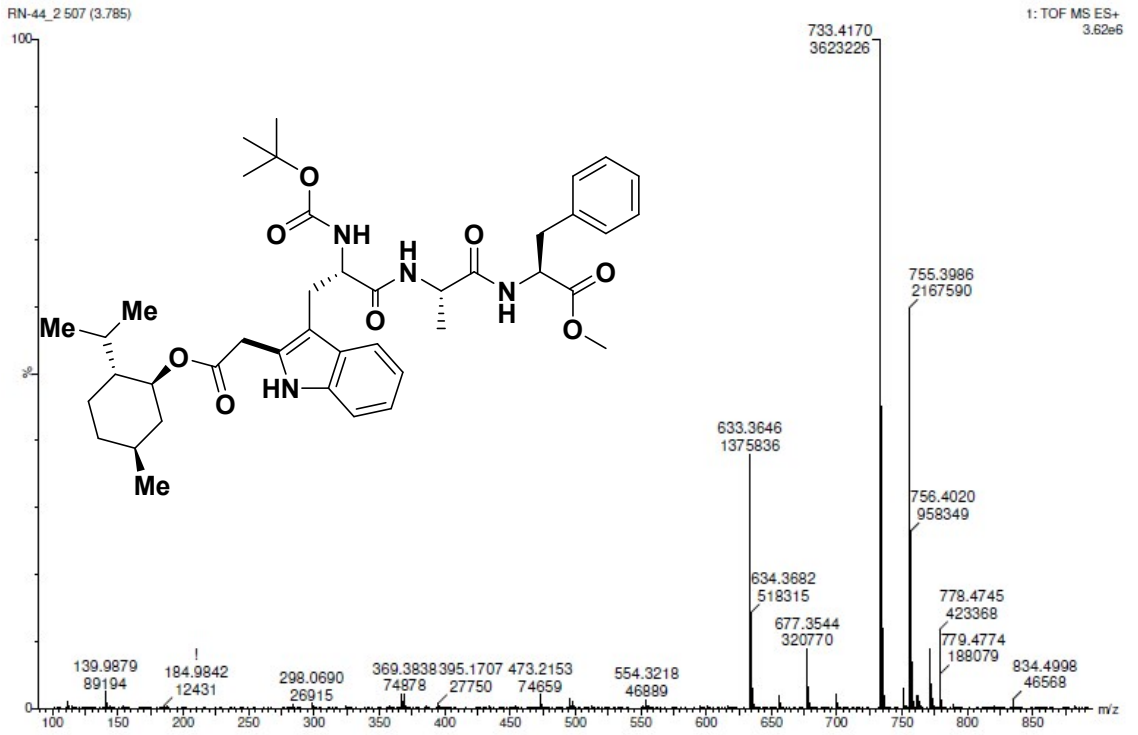


Figure S108. High Resolution Mass Spectra (HRMS) of **4j**

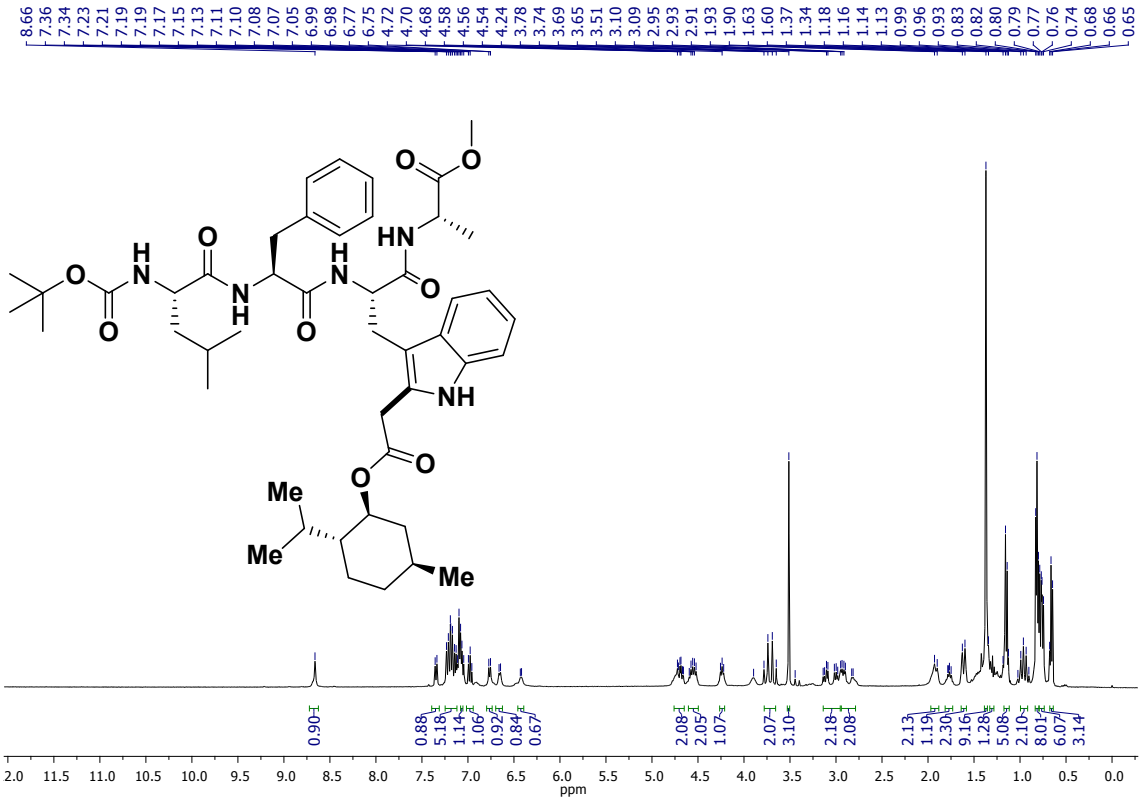
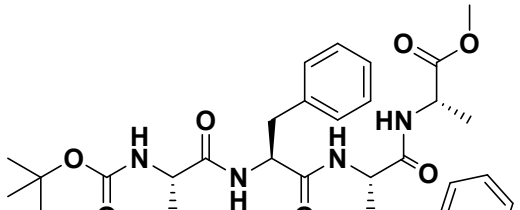


Figure S109. ^{1}H NMR (400 MHz, $CDCl_3$) of **4k**



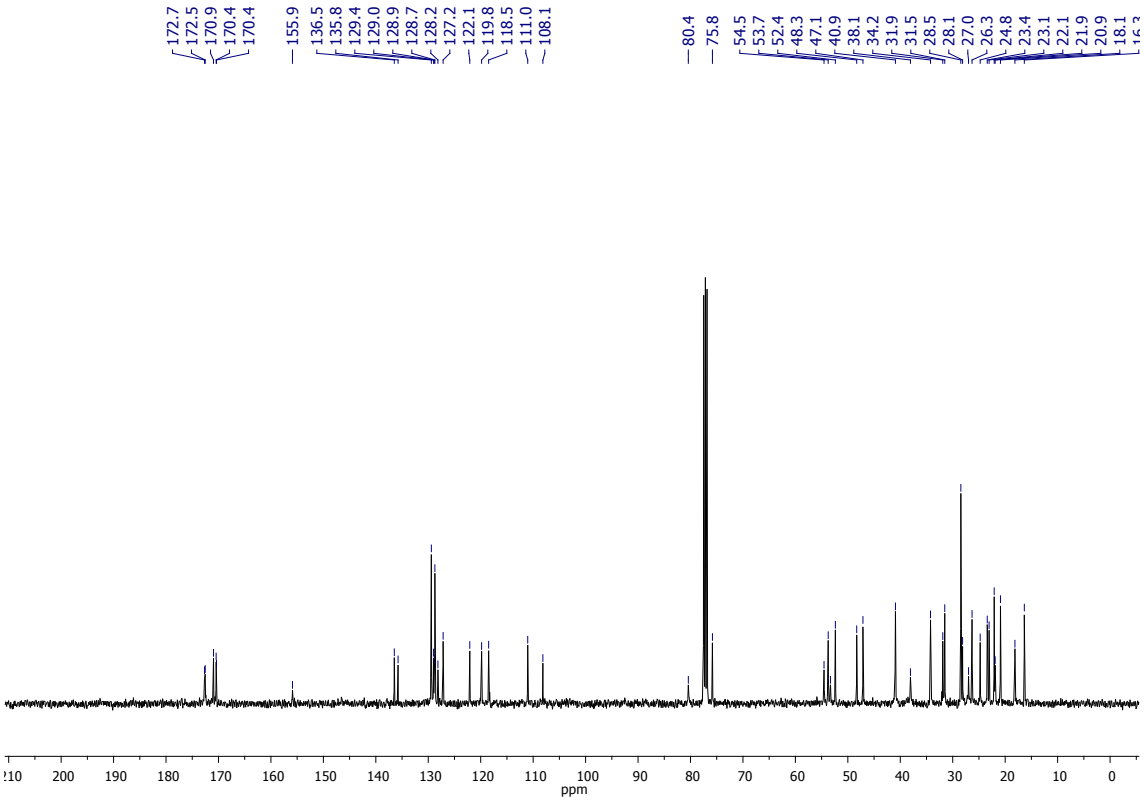


Figure S110. ^{13}C NMR (101 MHz, $CDCl_3$) of **4k**

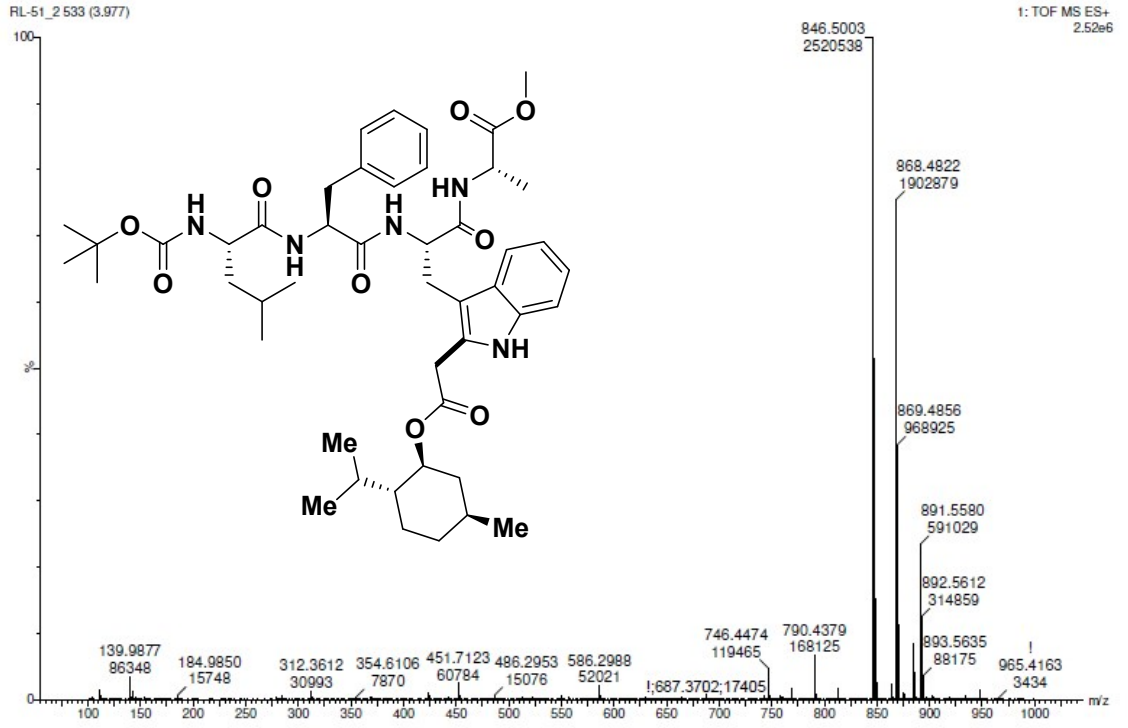


Figure S111. High Resolution Mass Spectra (HRMS) of **4k**

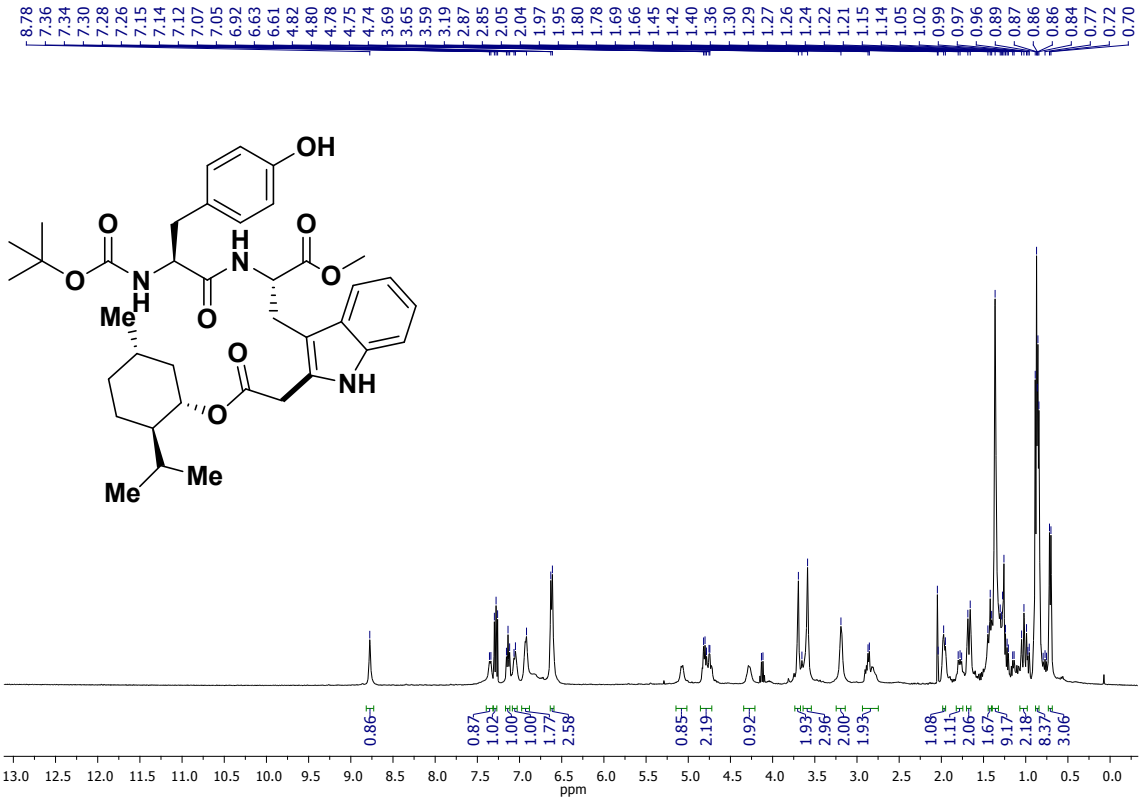


Figure S112. ^{1}H NMR (400 MHz, $CDCl_3$) of **4l**

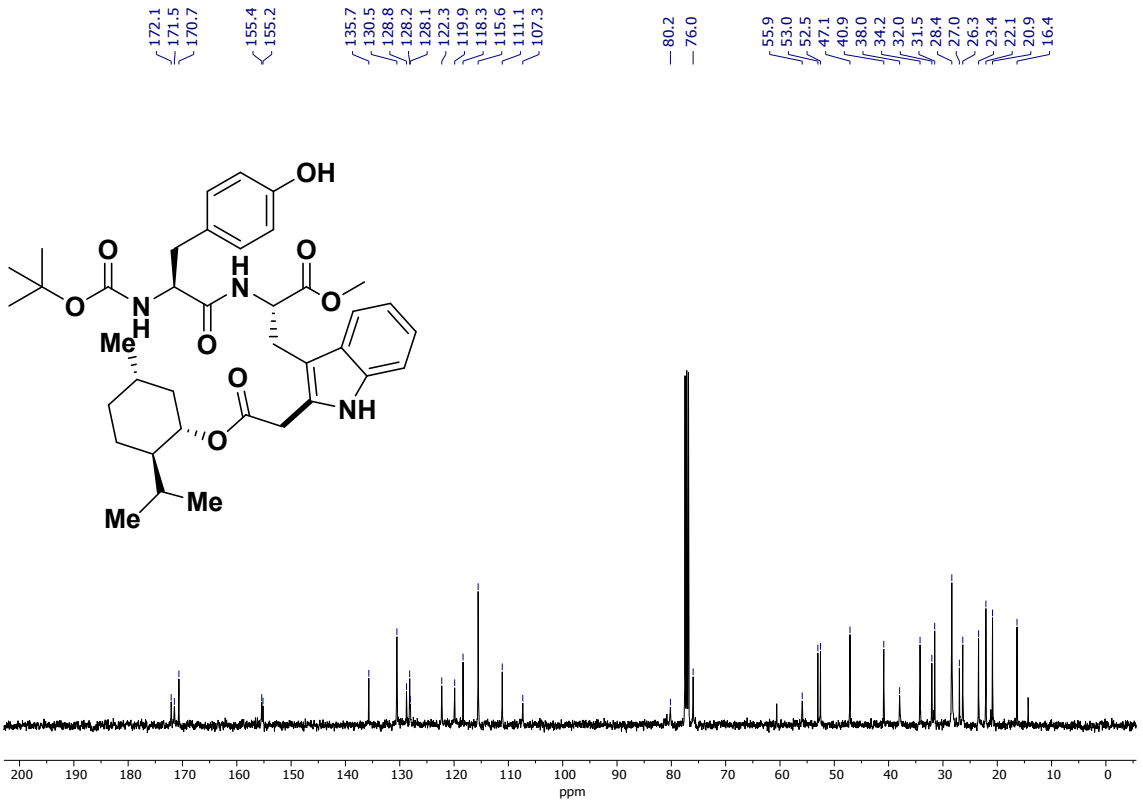


Figure S113. ^{13}C NMR (101 MHz, $CDCl_3$) of **4l**

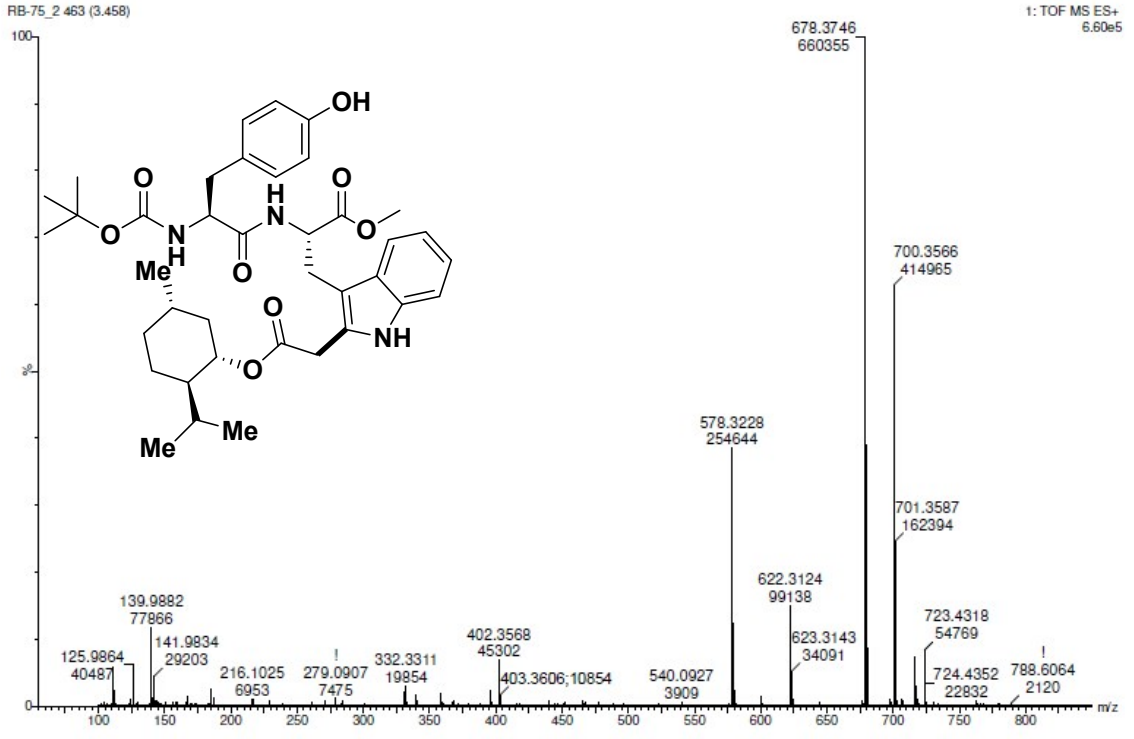


Figure S114. High Resolution Mass Spectra (HRMS) of **4l**

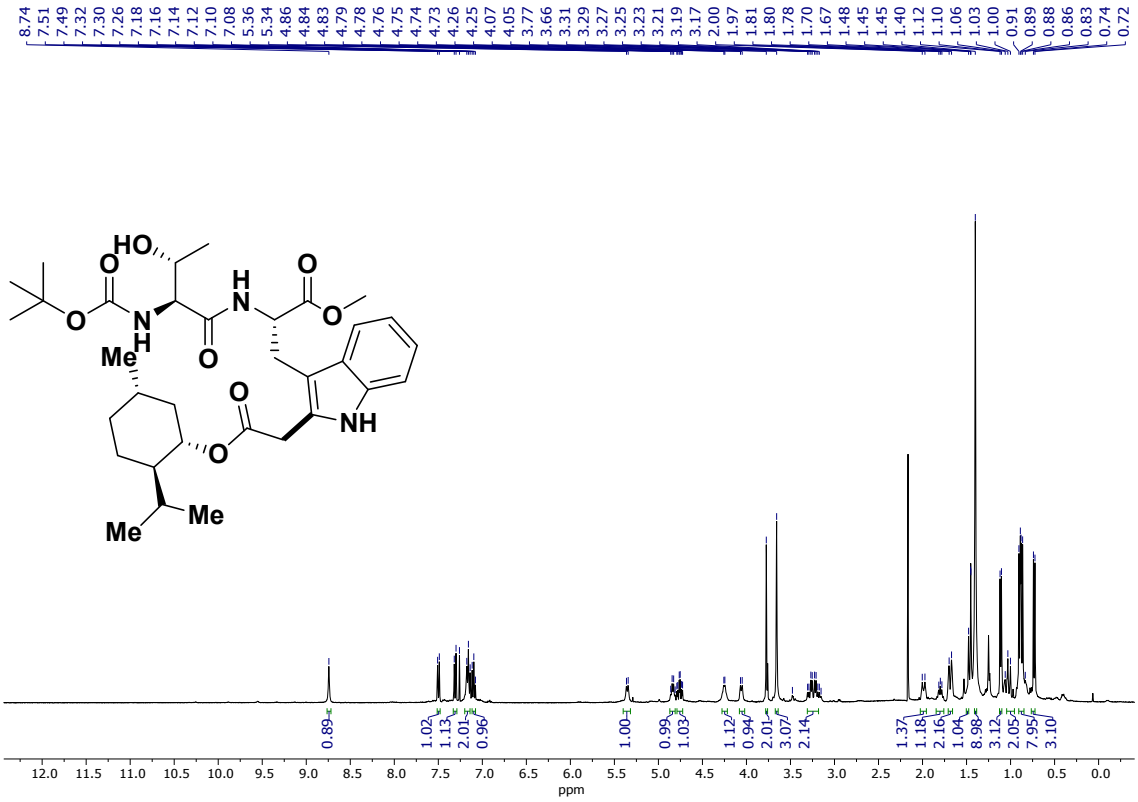


Figure S115. ^{1}H NMR (400 MHz, $CDCl_3$) of **4m**

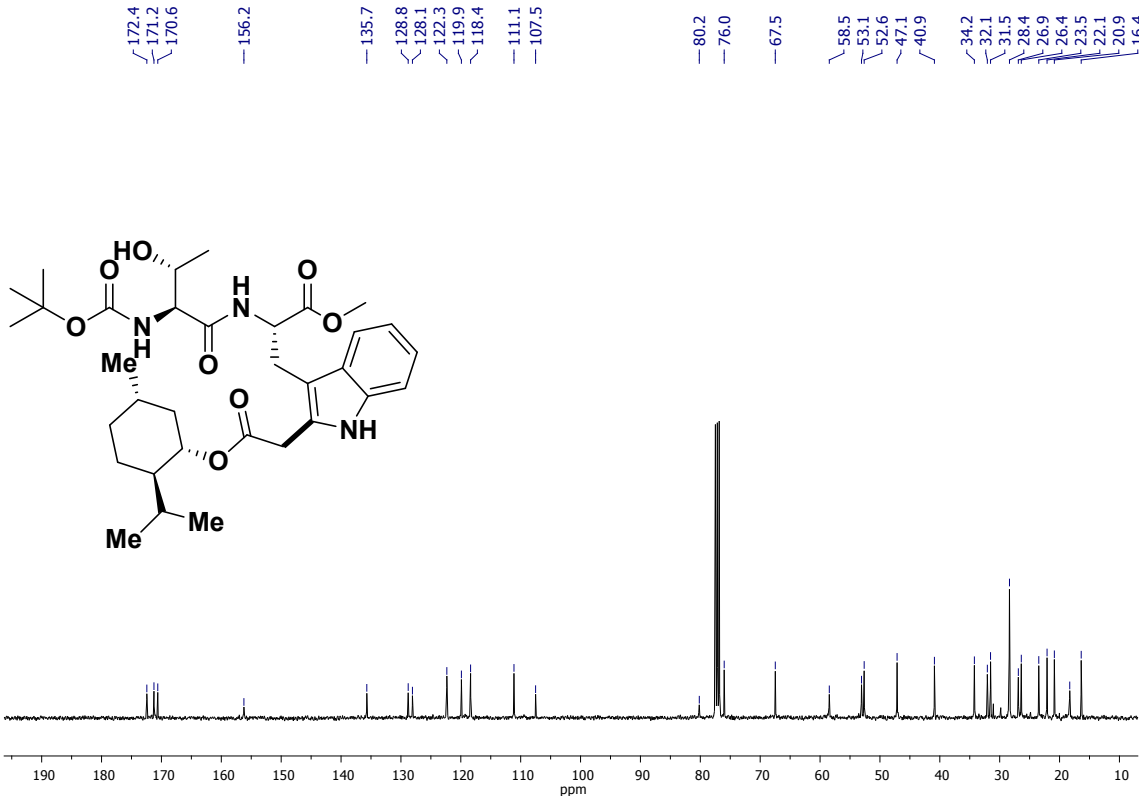


Figure S116. ^{13}C NMR (101 MHz, $CDCl_3$) of **4m**

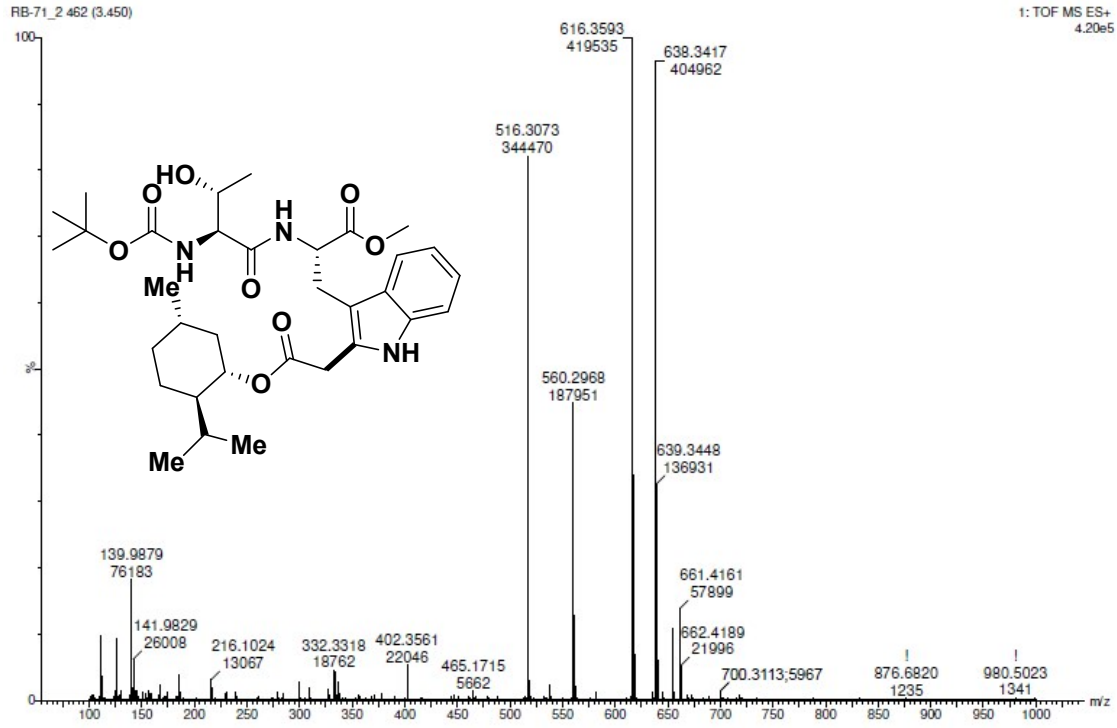


Figure S117. High Resolution Mass Spectra of **4m**

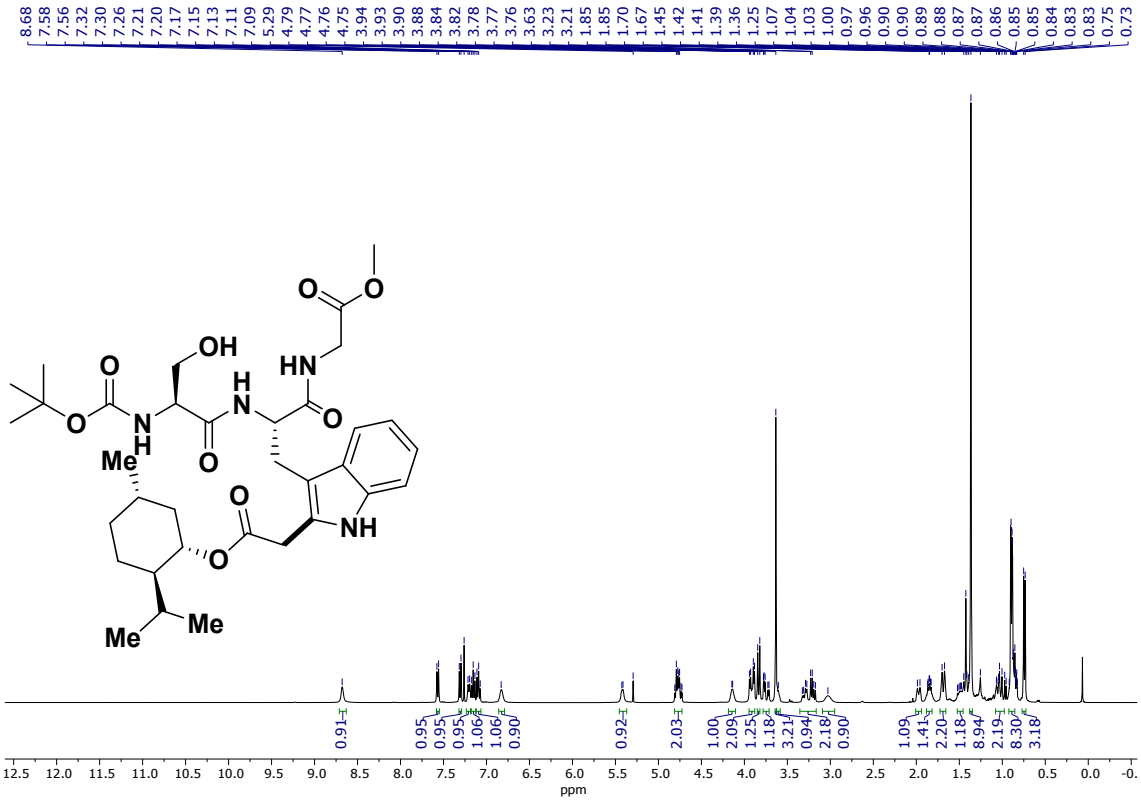


Figure S118. ^{1}H NMR (400 MHz, $CDCl_3$) of **4n**

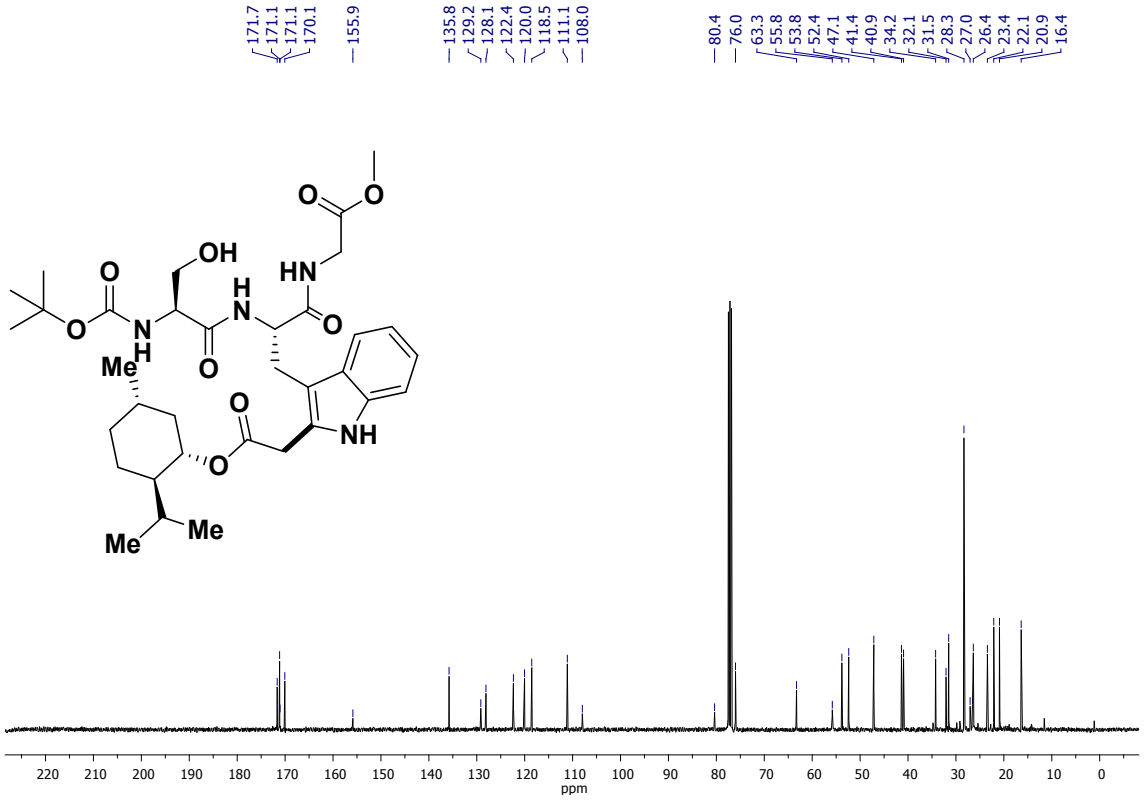


Figure S119. ^{13}C NMR (101 MHz, $CDCl_3$) of **4n**

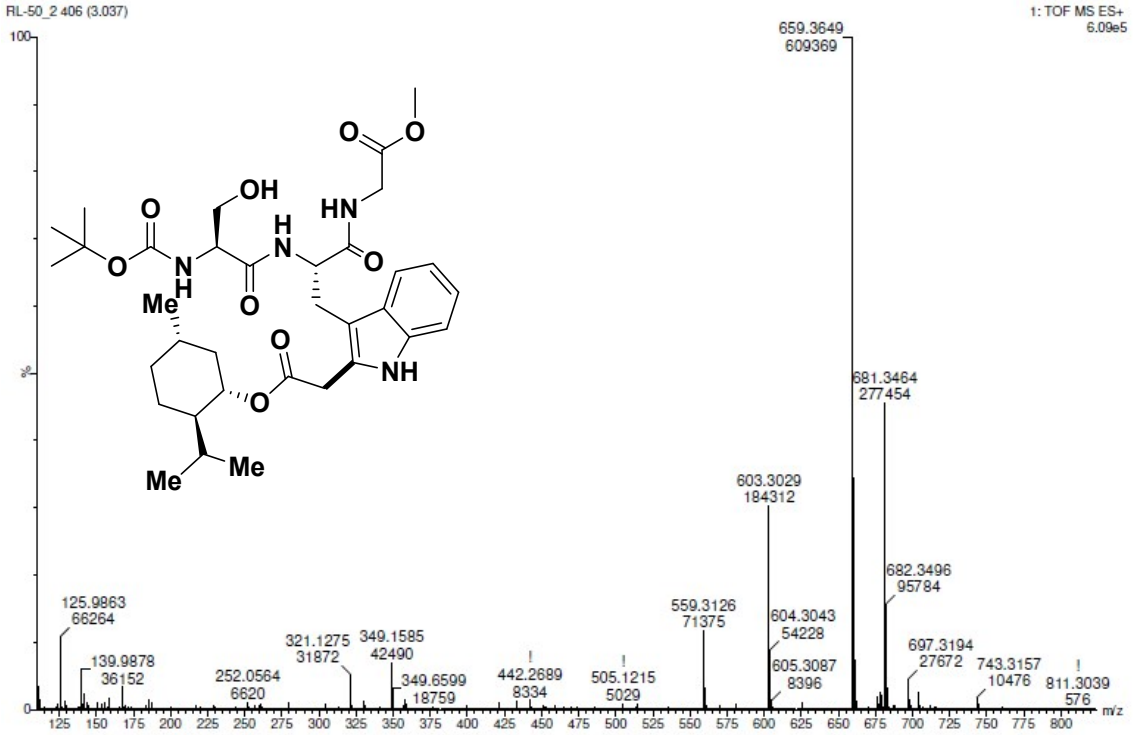


Figure S120. High Resolution Mass Spectra (HRMS) of **4n**

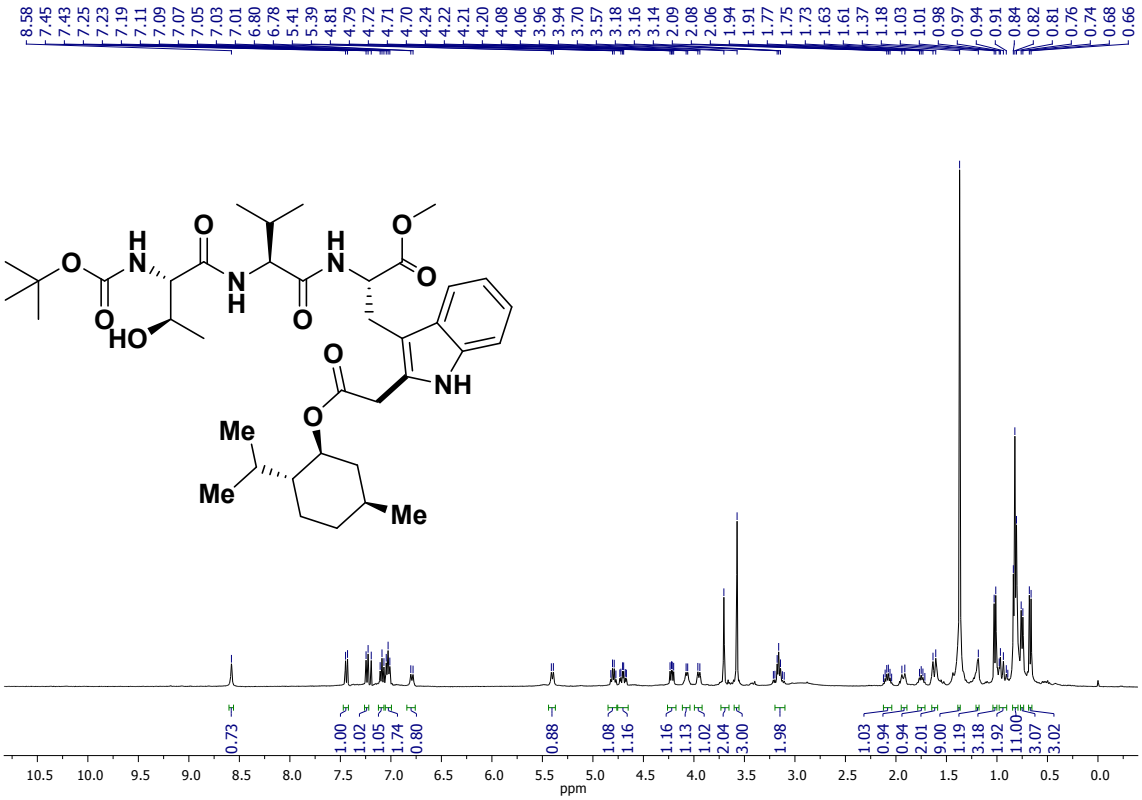


Figure S121. ^{1}H NMR (400 MHz, $CDCl_3$) of **4o**

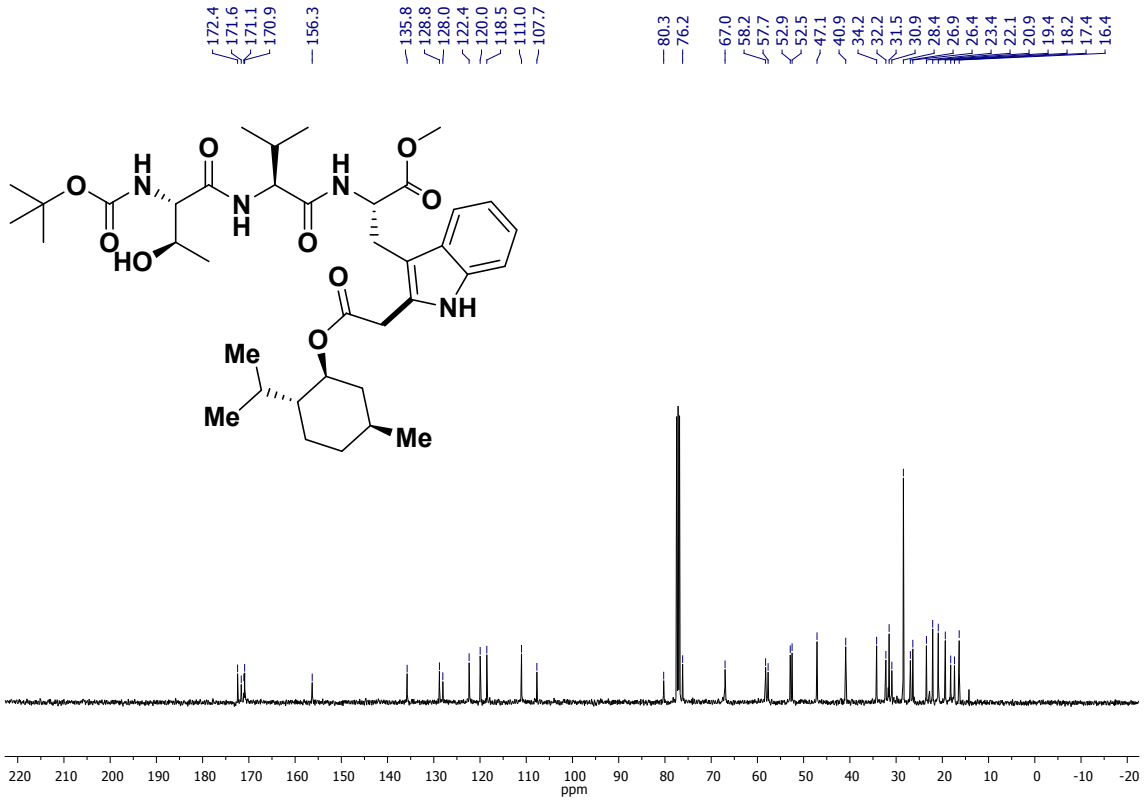


Figure S122. ^{13}C NMR (101 MHz, $CDCl_3$) of **4o**

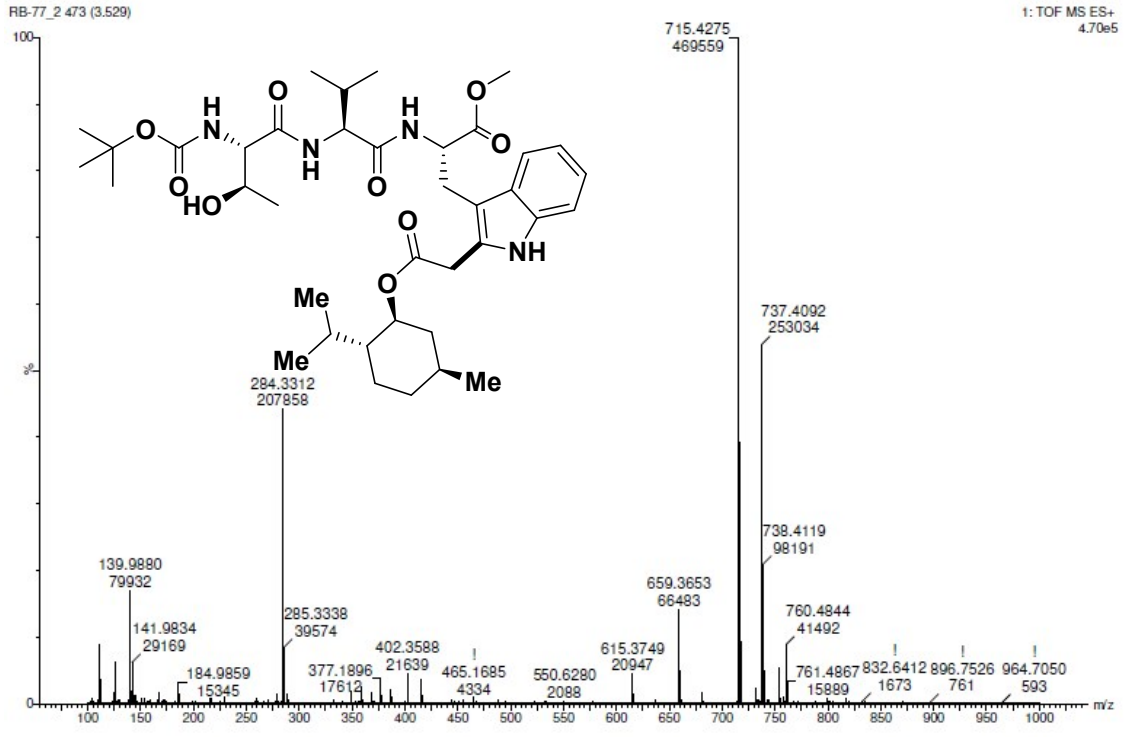


Figure S123. High Resolution Mass Spectra (HRMS) of **4o**

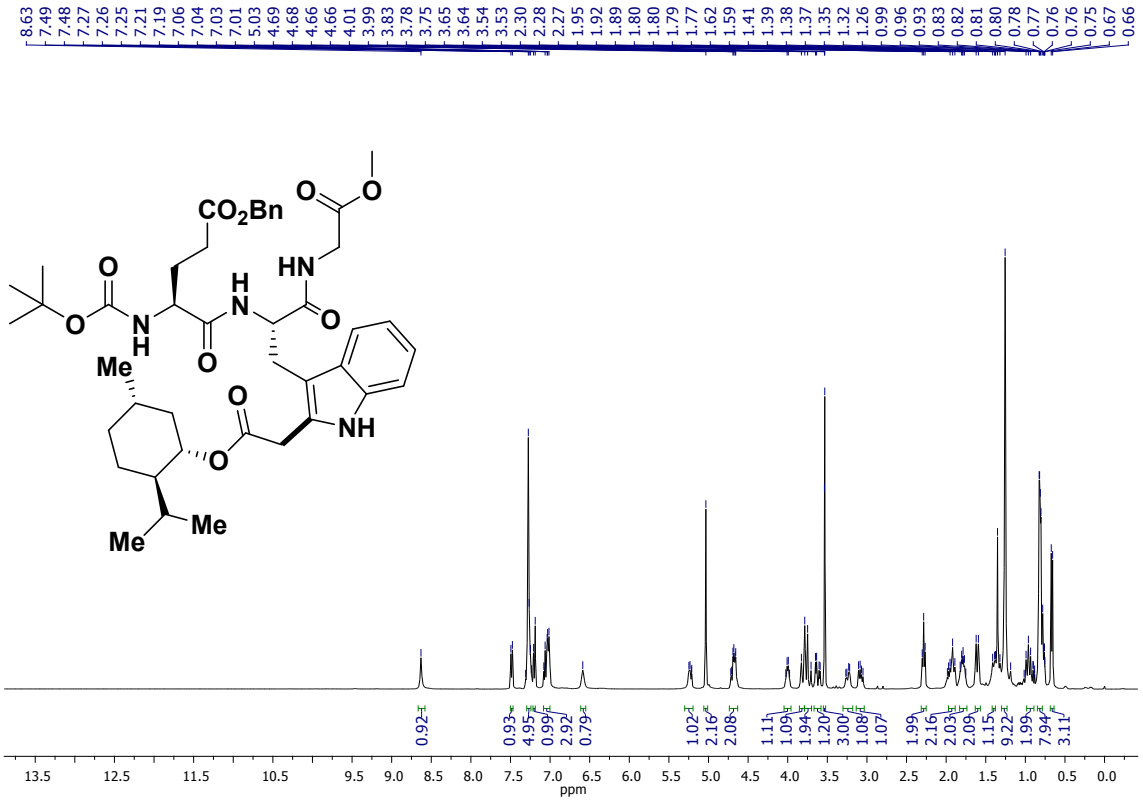


Figure S124. ^{1}H NMR (400 MHz, $CDCl_3$) of **4p**

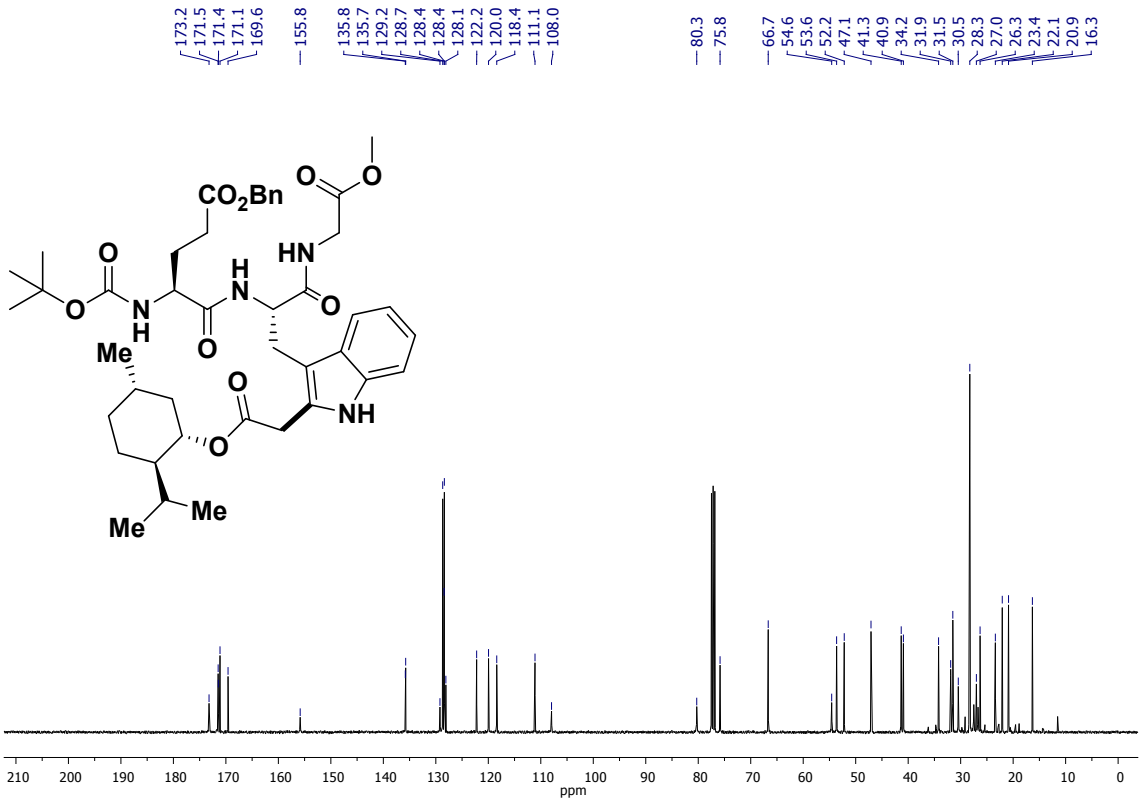


Figure S125. ^{13}C NMR (101 MHz, $CDCl_3$) of **4p**

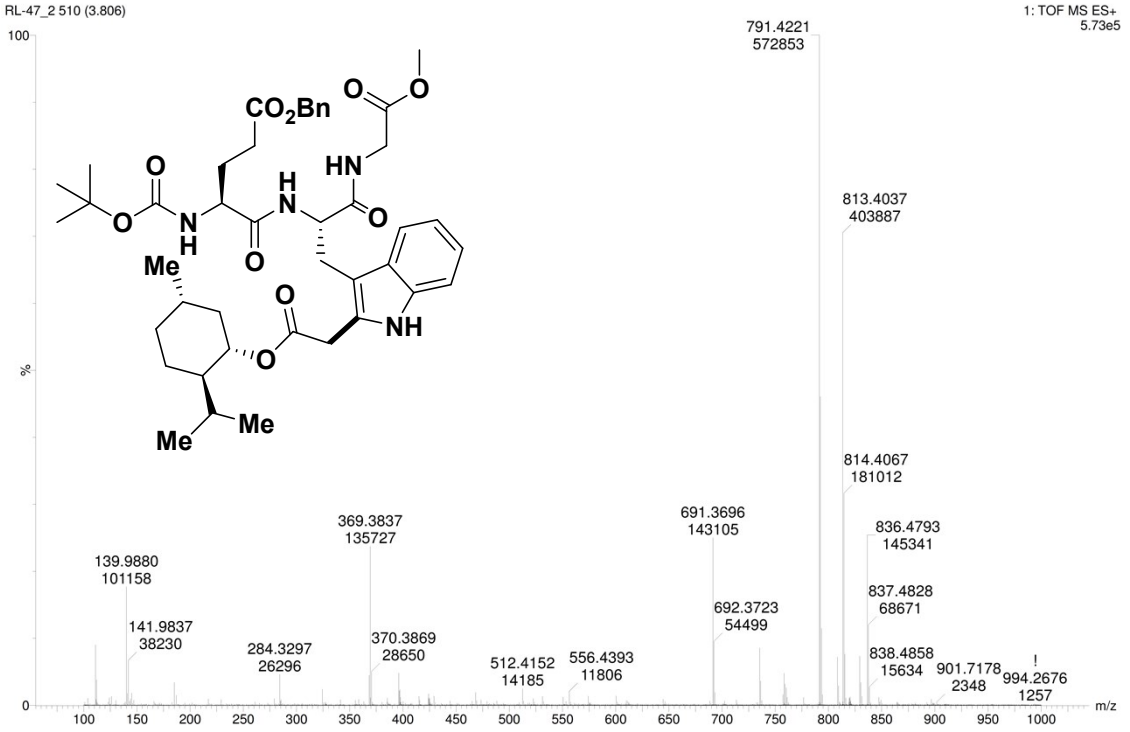


Figure S126. High Resolution Mass Spectra (HRMS) of **4p**

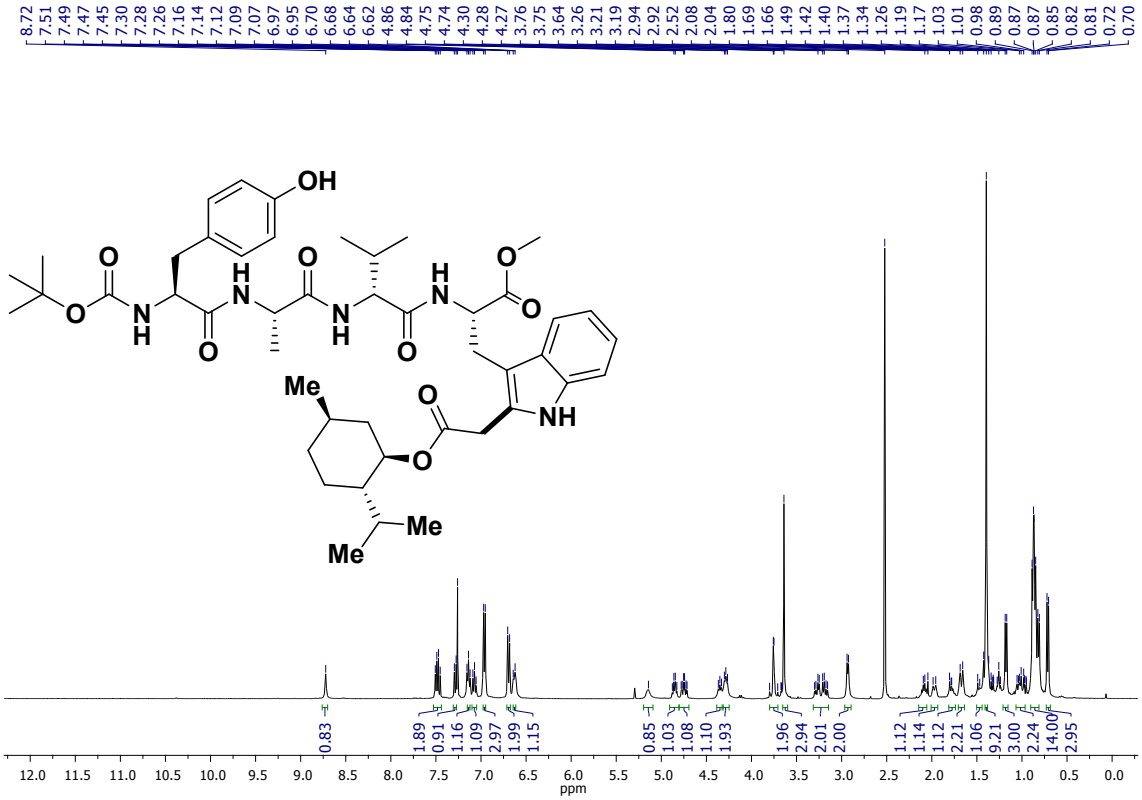


Figure S127. ^{1}H NMR (400 MHz, $CDCl_3$) of **4q**

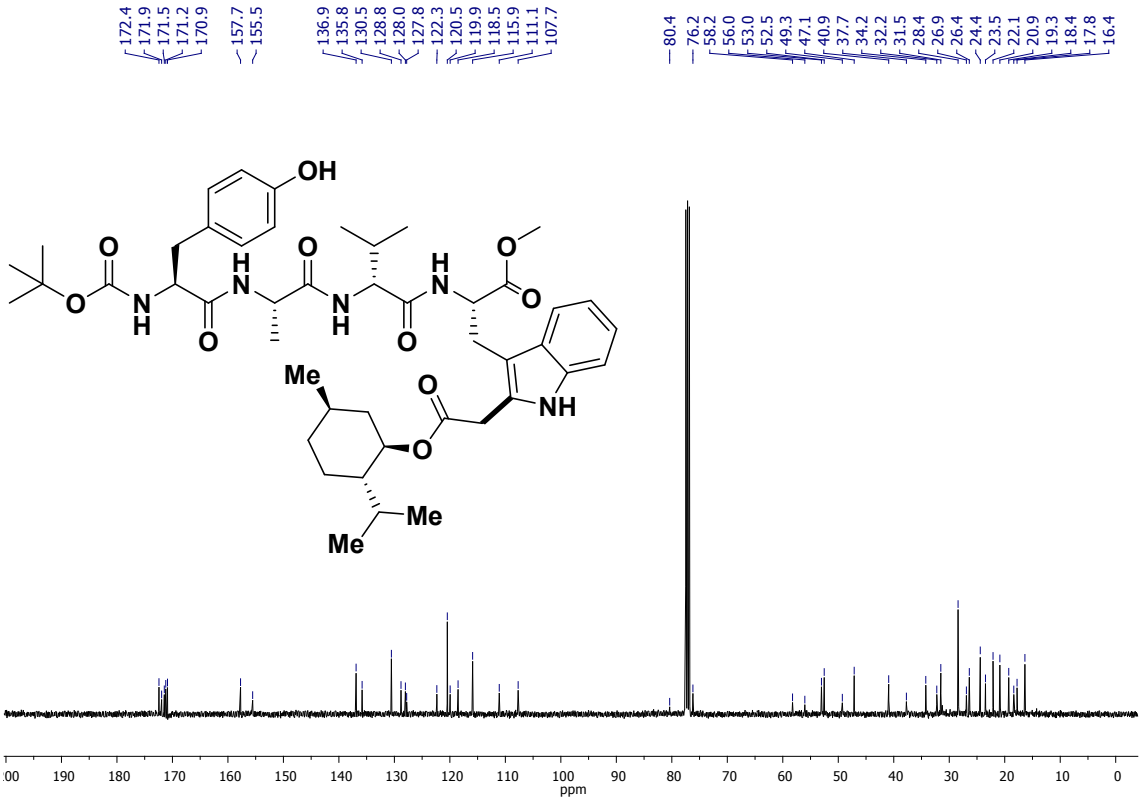


Figure S128. ^{13}C NMR (101 MHz, $CDCl_3$) of **4q**

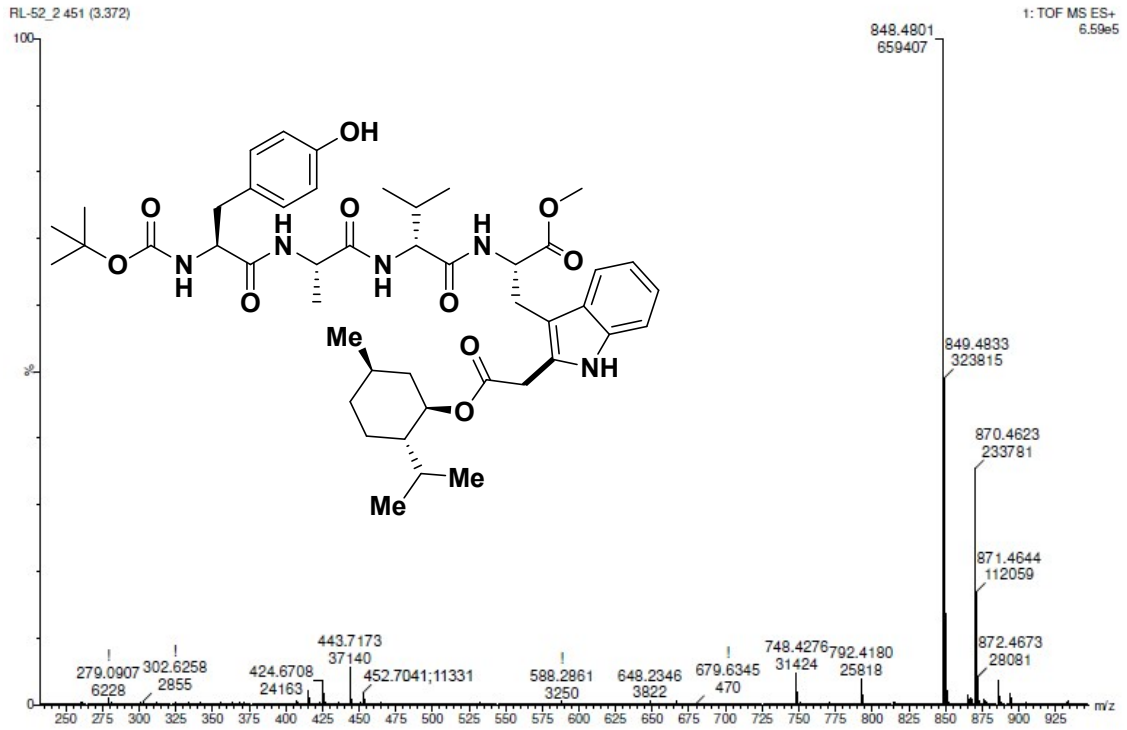


Figure S129. High Resolution Mass Spectra (HRMS) of **4q**

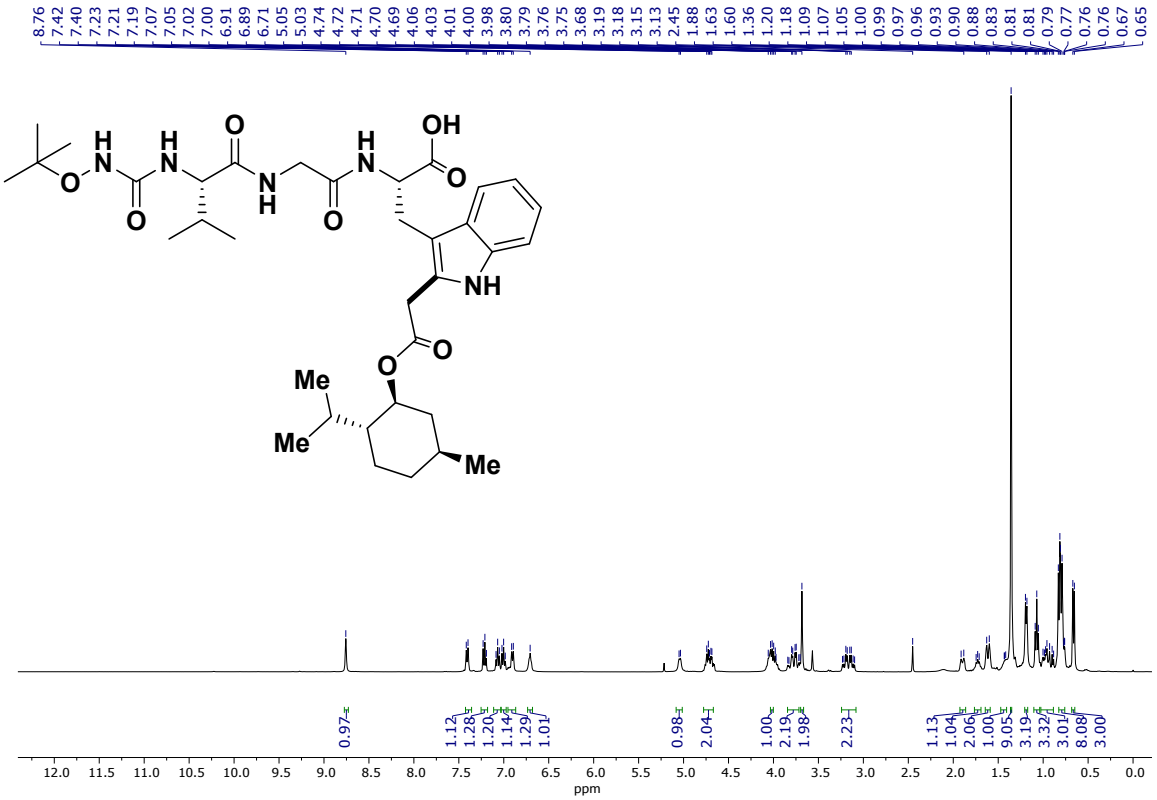


Figure S130. ^{1}H NMR (400 MHz, $CDCl_3$) of **4r**

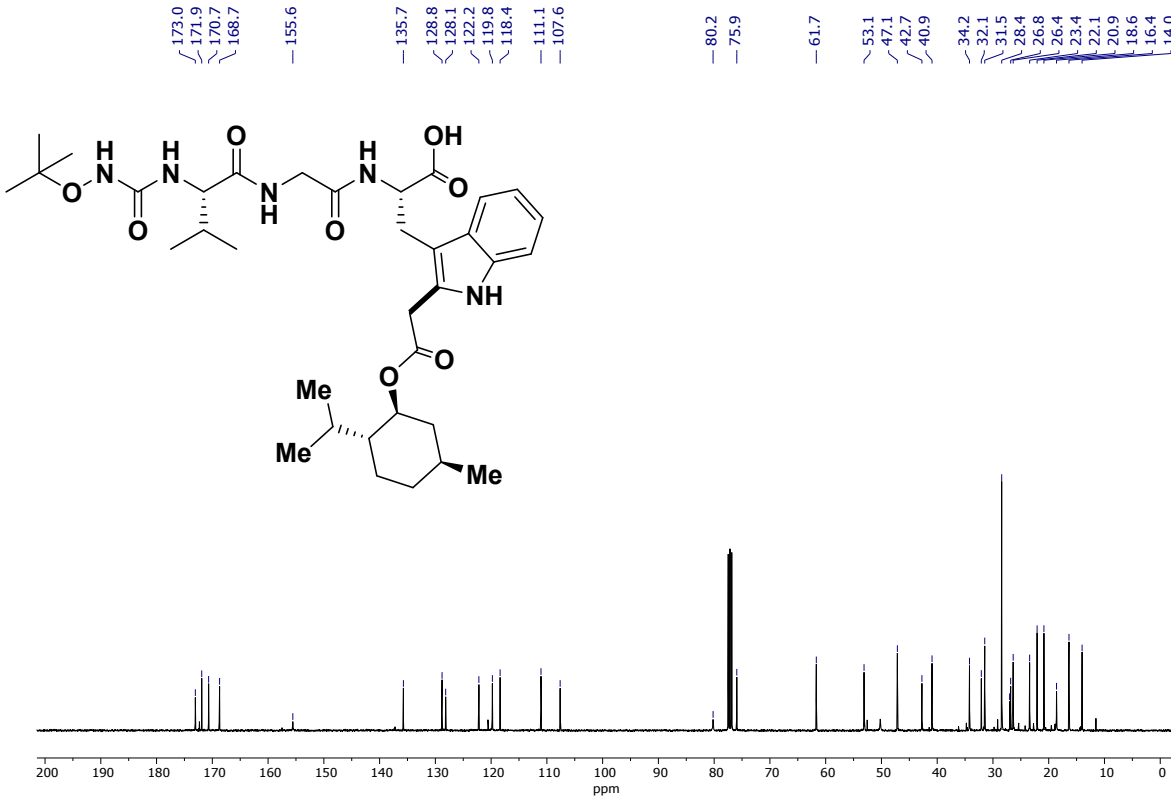


Figure S131. ^{13}C NMR (101 MHz, $CDCl_3$) of **4r**

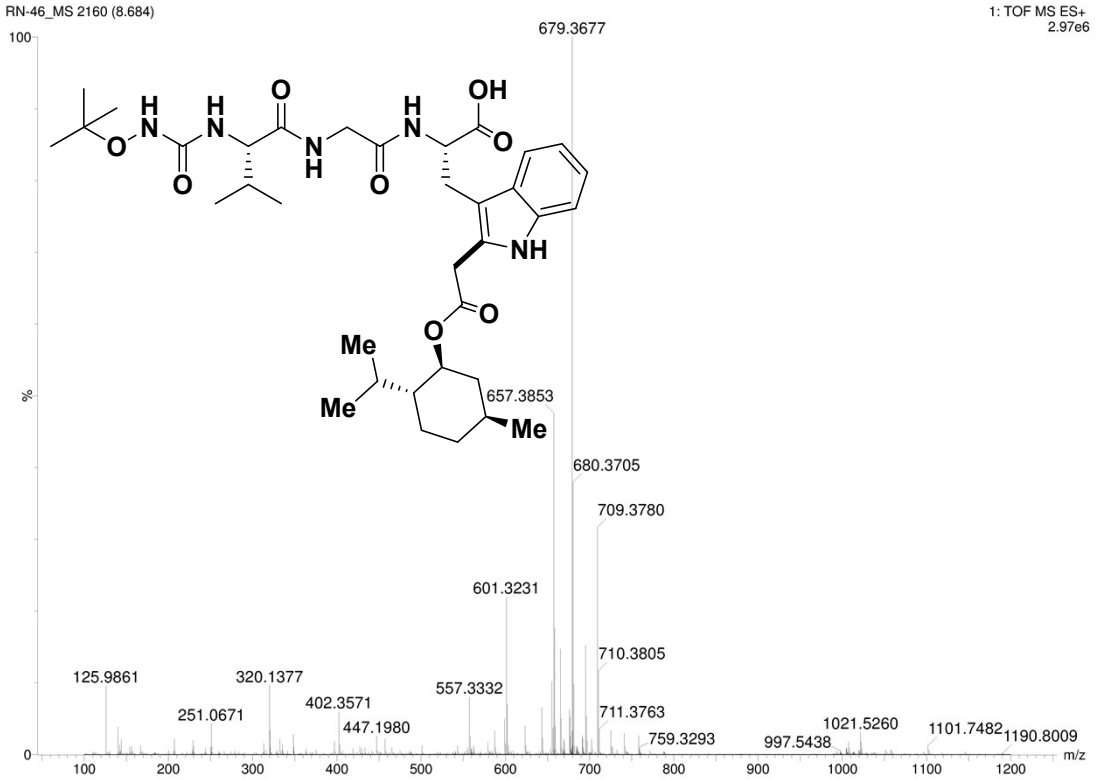


Figure S132. High Resolution Mass Spectra (HRMS) of **4r**

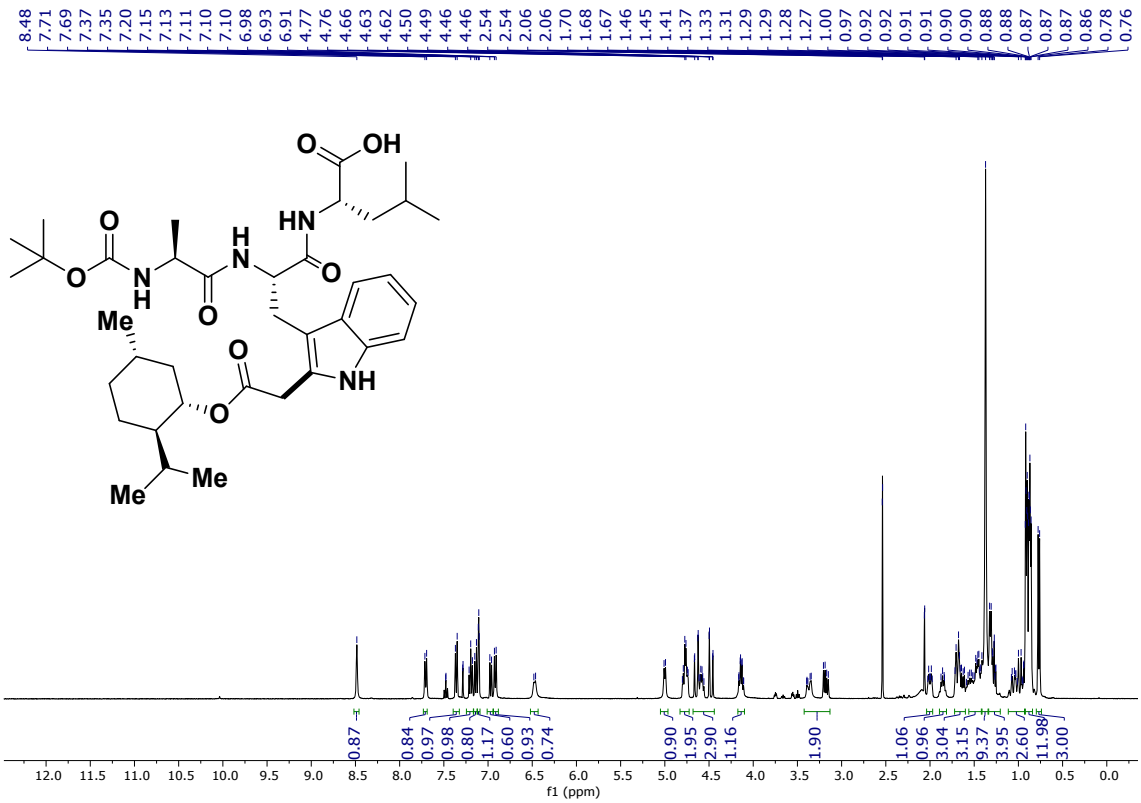


Figure S133. ^{1}H NMR (400 MHz, $CDCl_3$) of **4s**

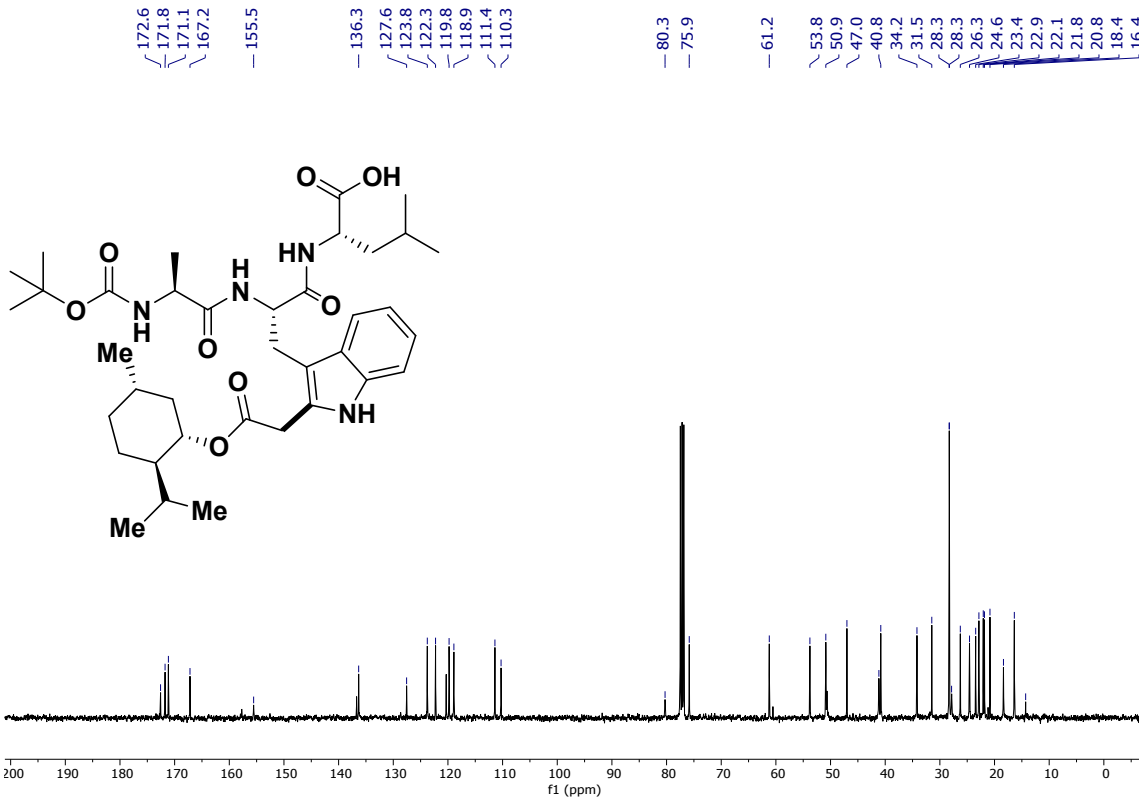


Figure S134. ^{13}C NMR (101 MHz, $CDCl_3$) of **4s**

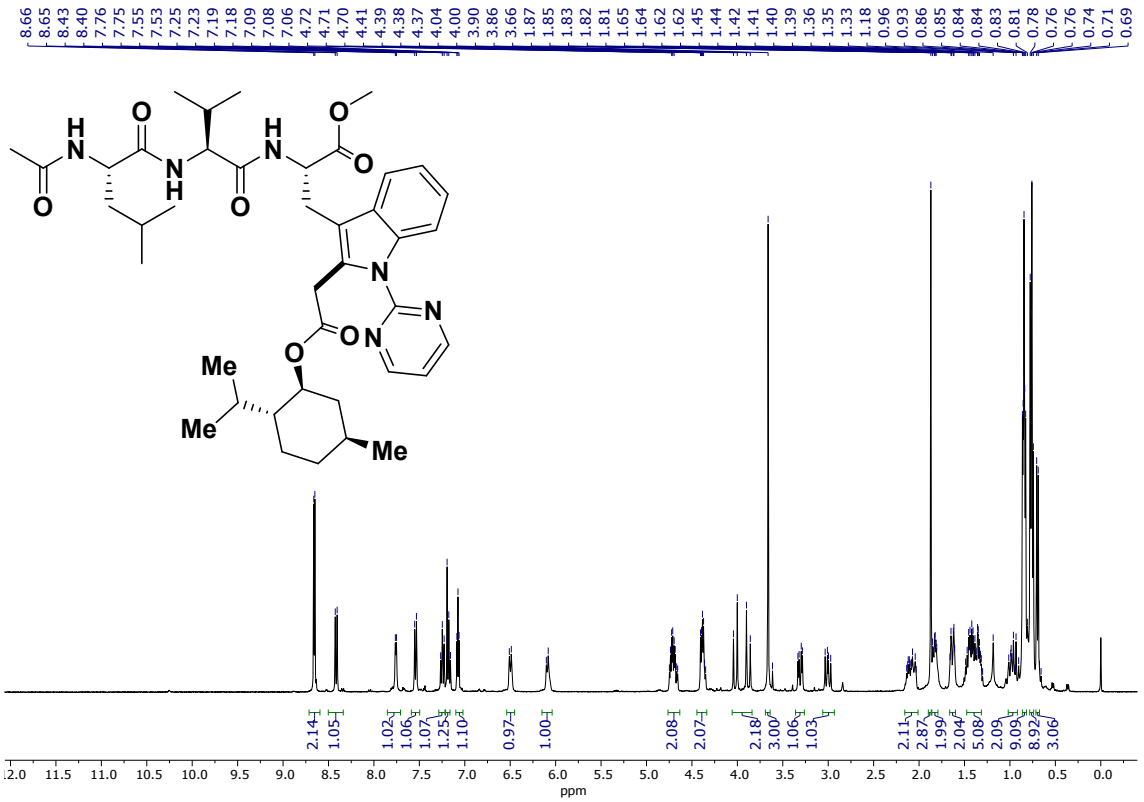


Figure S135. ^{1}H NMR (400 MHz, $CDCl_3$) of **4t**

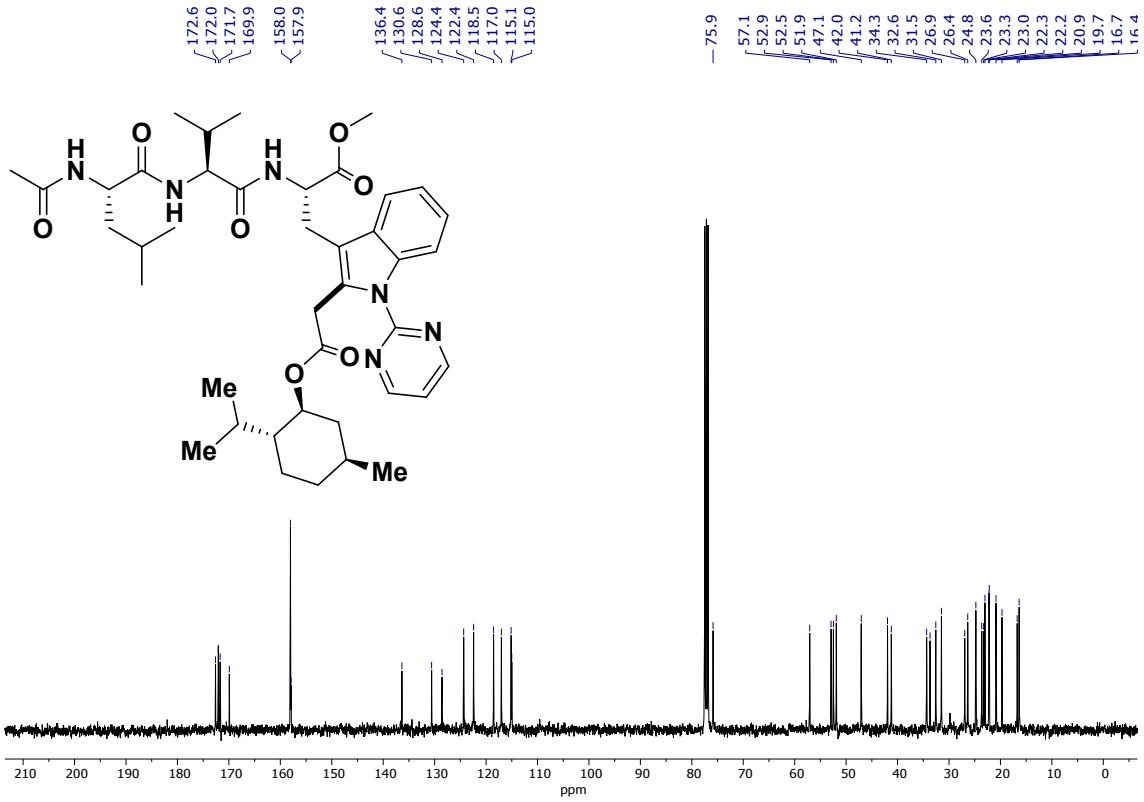


Figure S136. ^{13}C NMR (101 MHz, $CDCl_3$) of **4t**

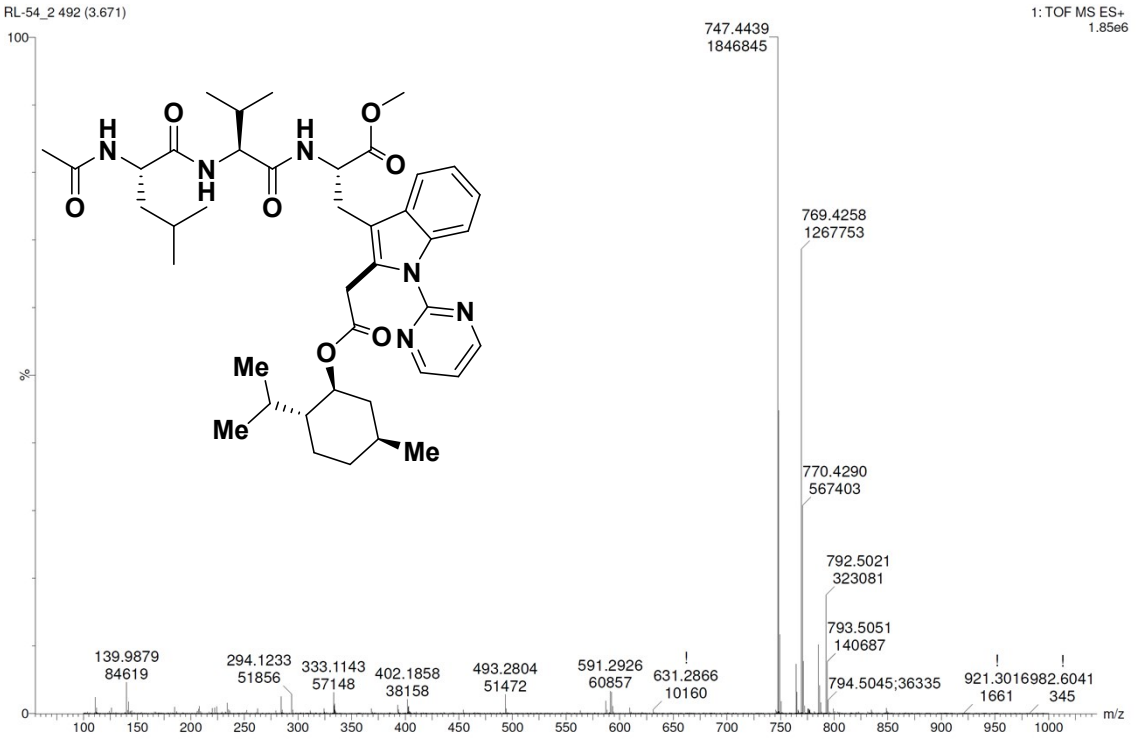


Figure S137. High Resolution Mass Spectra (HRMS) of **4t**

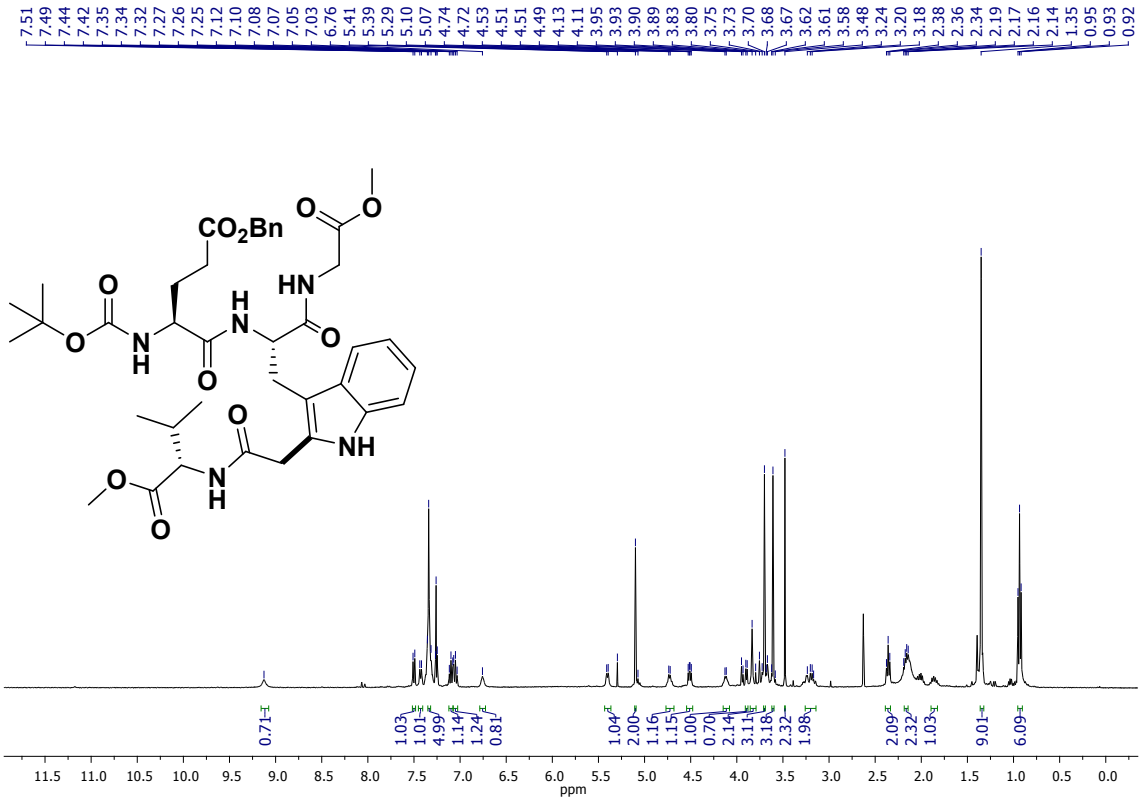


Figure S138. ^{1}H NMR (400 MHz, $CDCl_3$) of **4u**

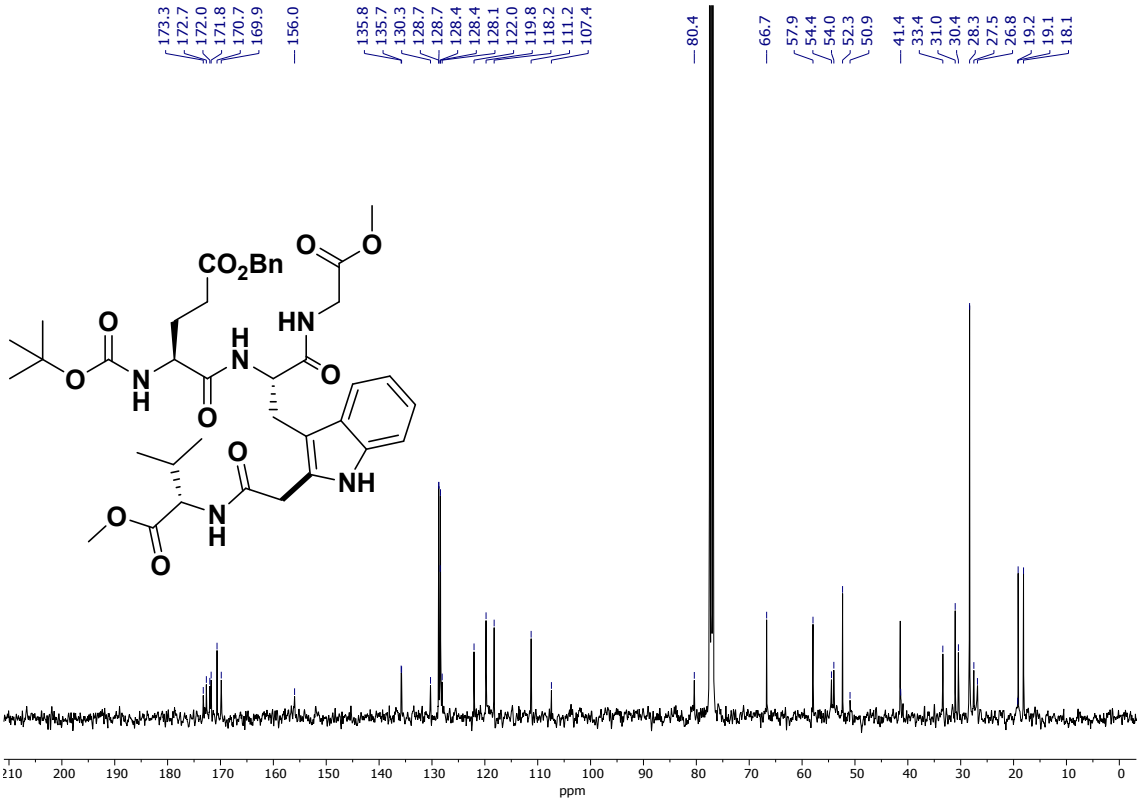


Figure S139. ^{13}C NMR (101 MHz, $CDCl_3$) of **4u**

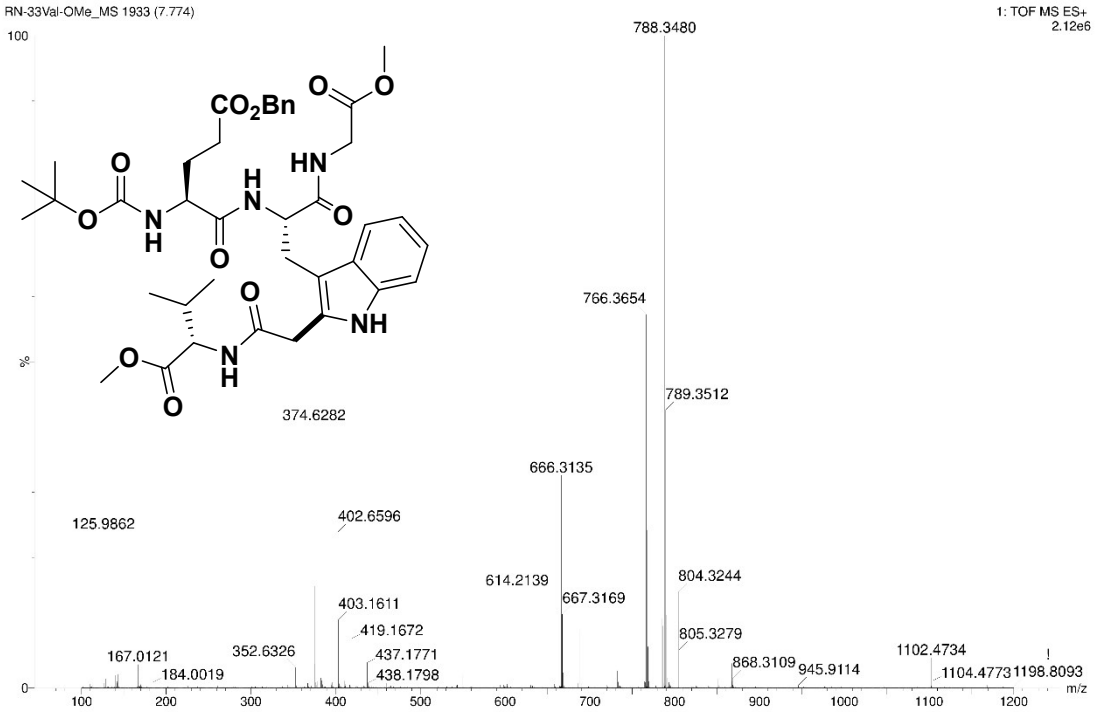


Figure S140. High Resolution Mass Spectra (HRMS) of **4u**

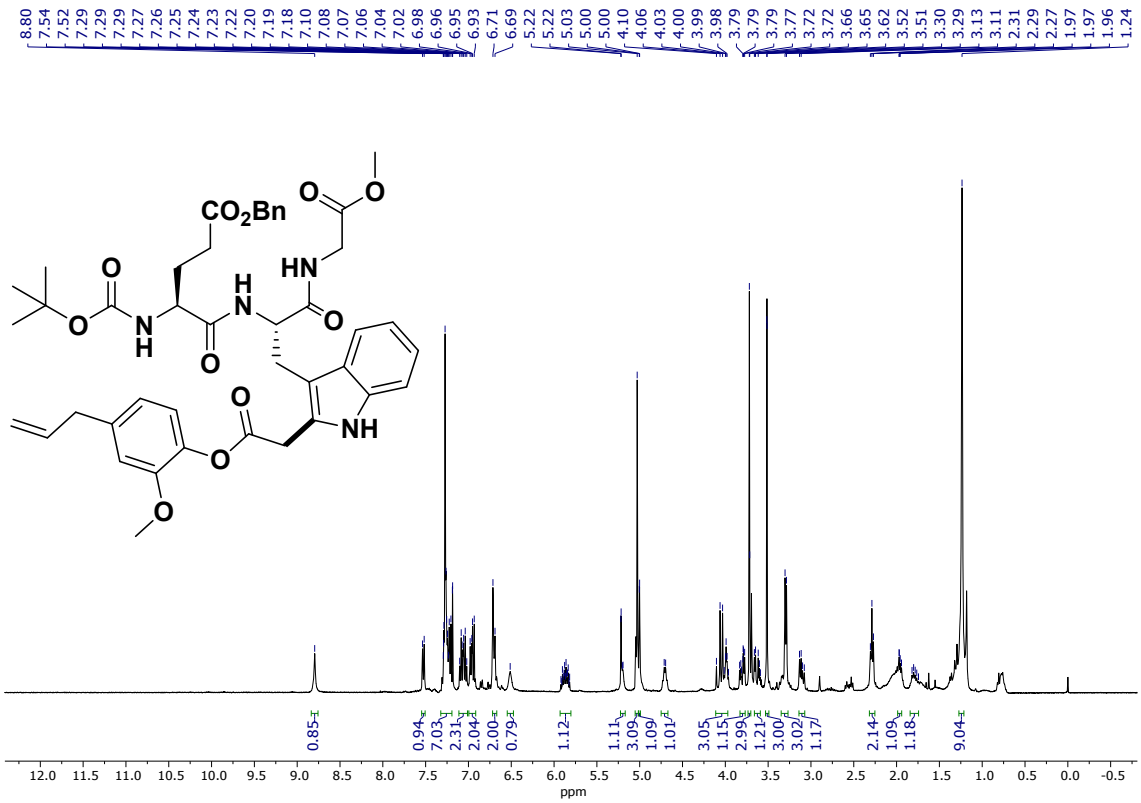


Figure S141. ^{1}H NMR (400 MHz, $CDCl_3$) of **4v**

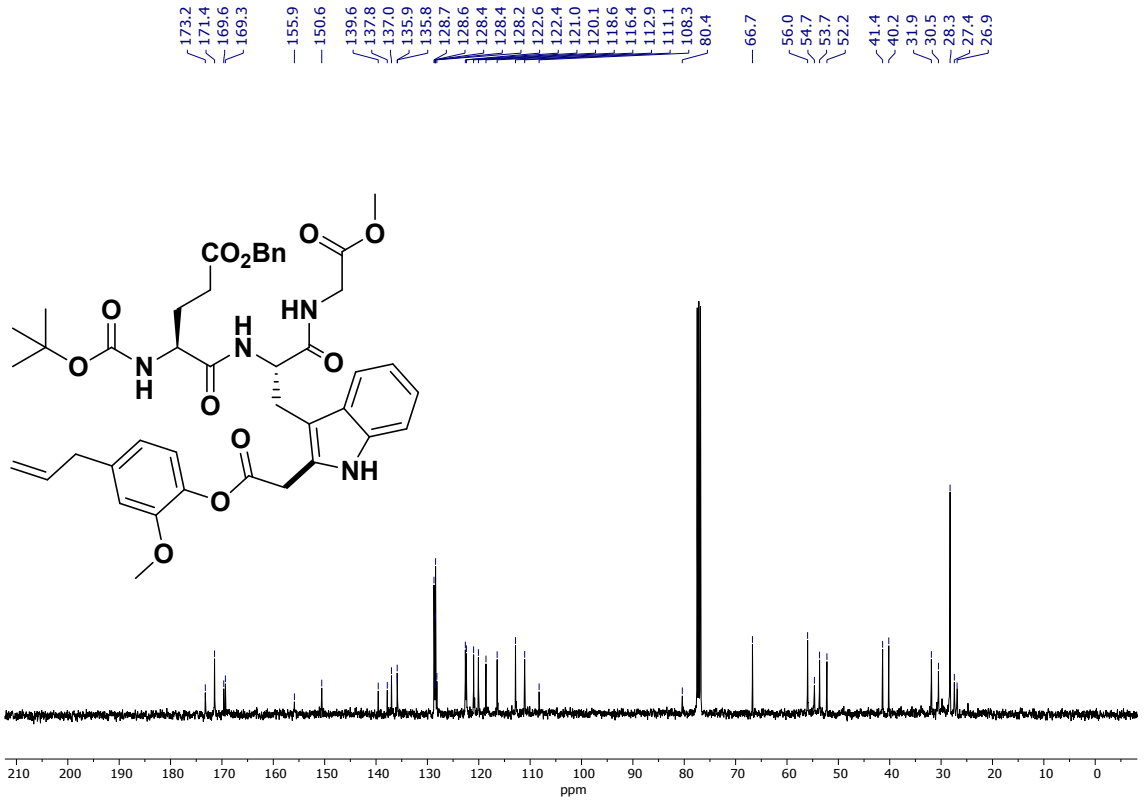


Figure S142. ^{13}C NMR (101 MHz, $CDCl_3$) of **4v**

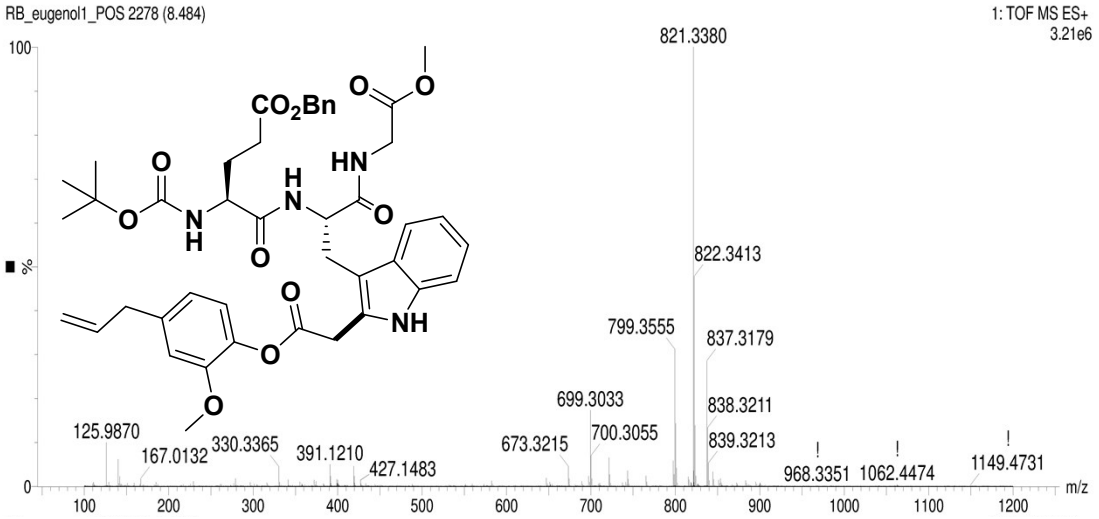


Figure S143. High Resolution Mass Spectra (HRMS) of **4v**

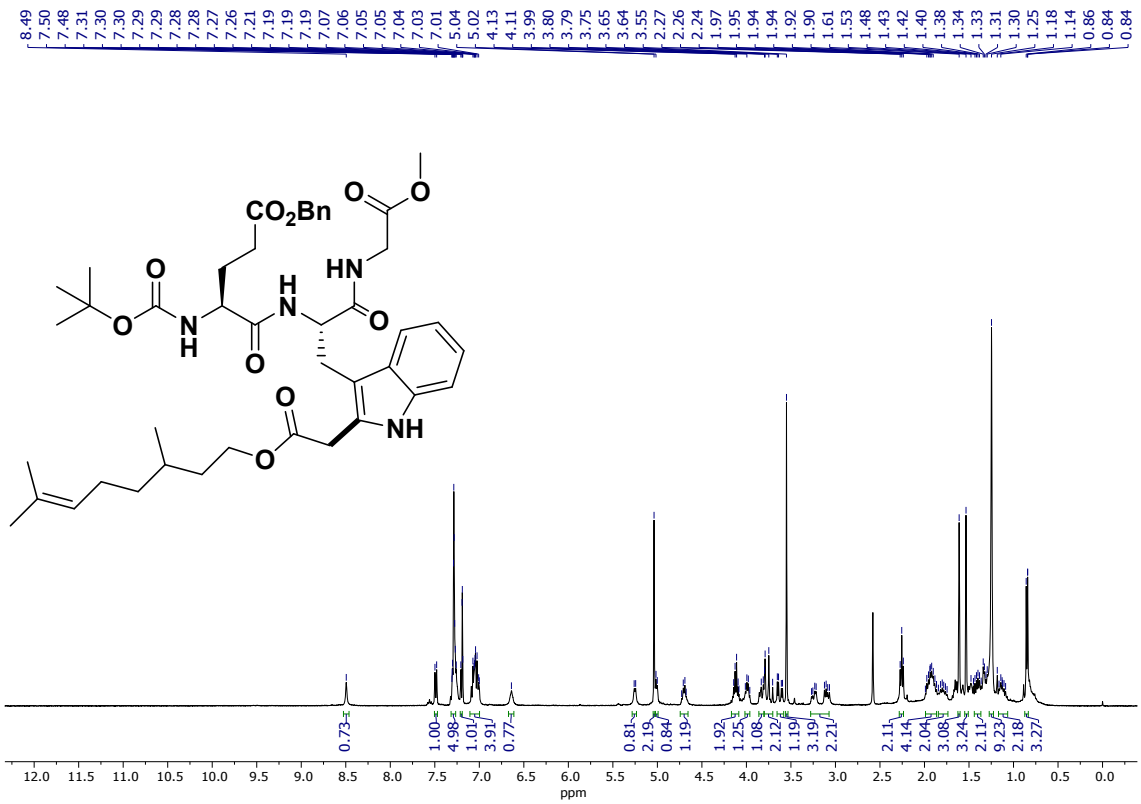


Figure S144. ^{1}H NMR (400 MHz, $CDCl_3$) of **4x**

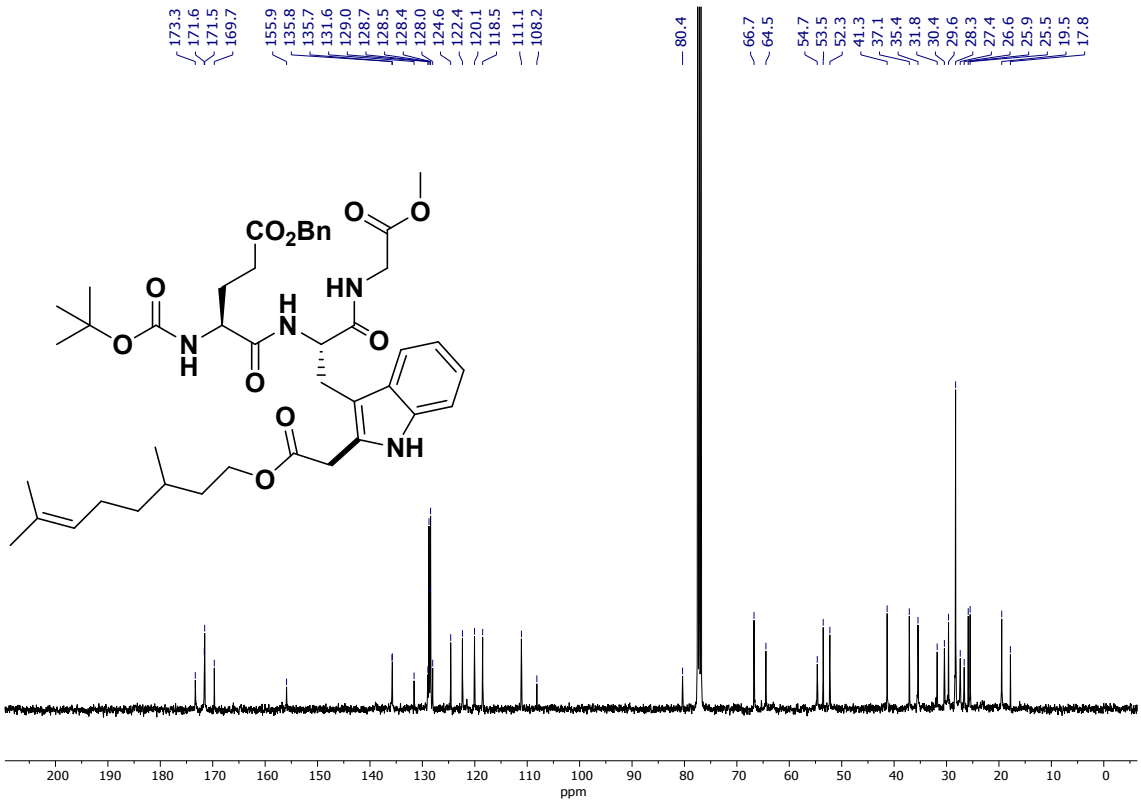


Figure S145. ^{13}C NMR (101 MHz, $CDCl_3$) of **4x**

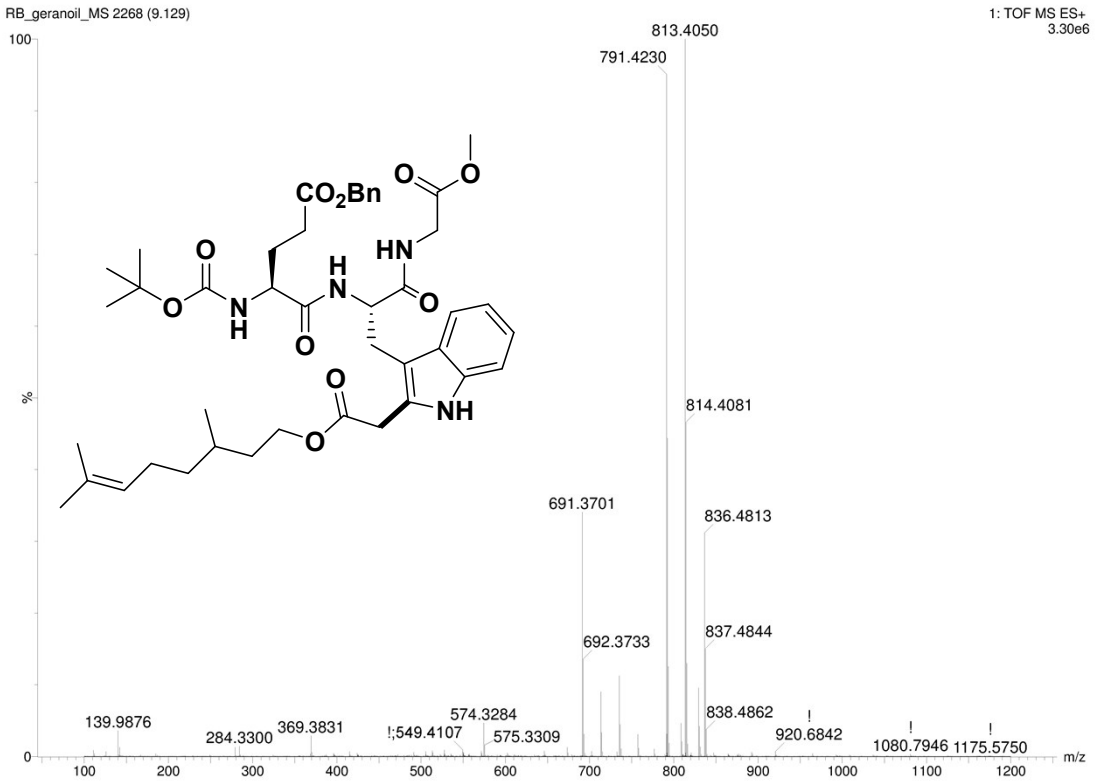


Figure S146. High Resolution Mass Spectra (HRMS) of **4x**

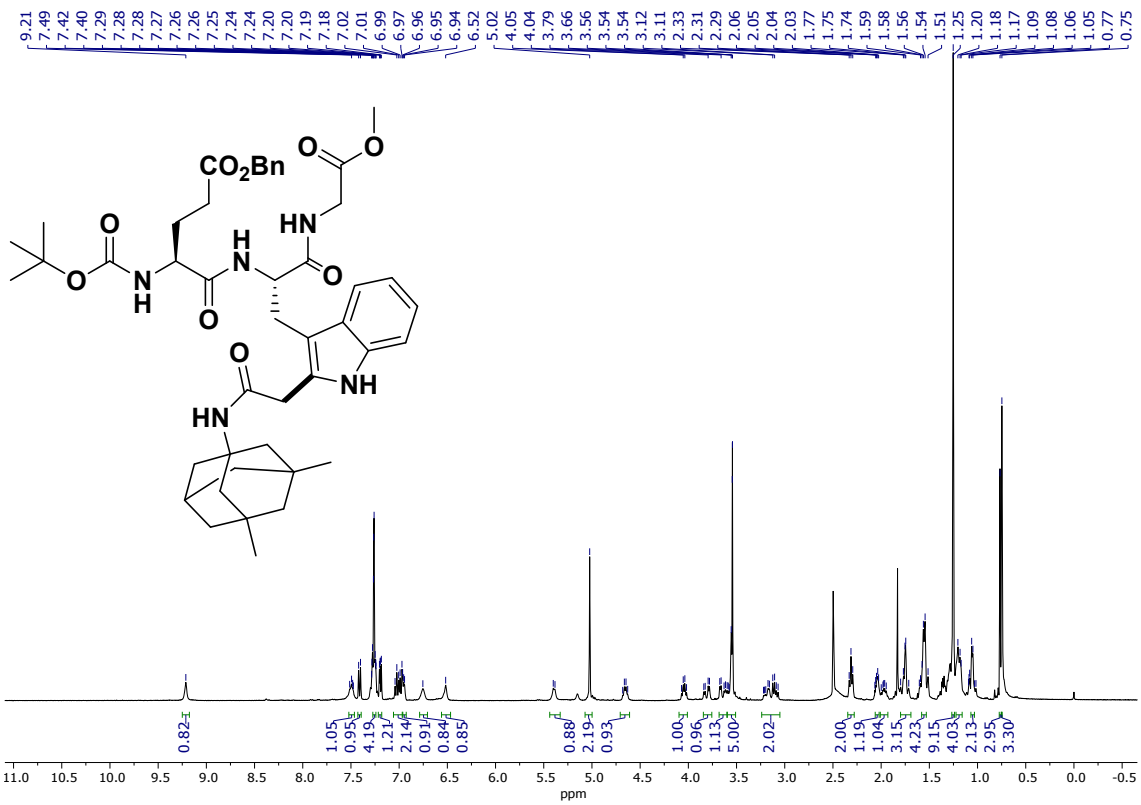


Figure S147. ^{1}H NMR (400 MHz, $CDCl_3$) of **4y**

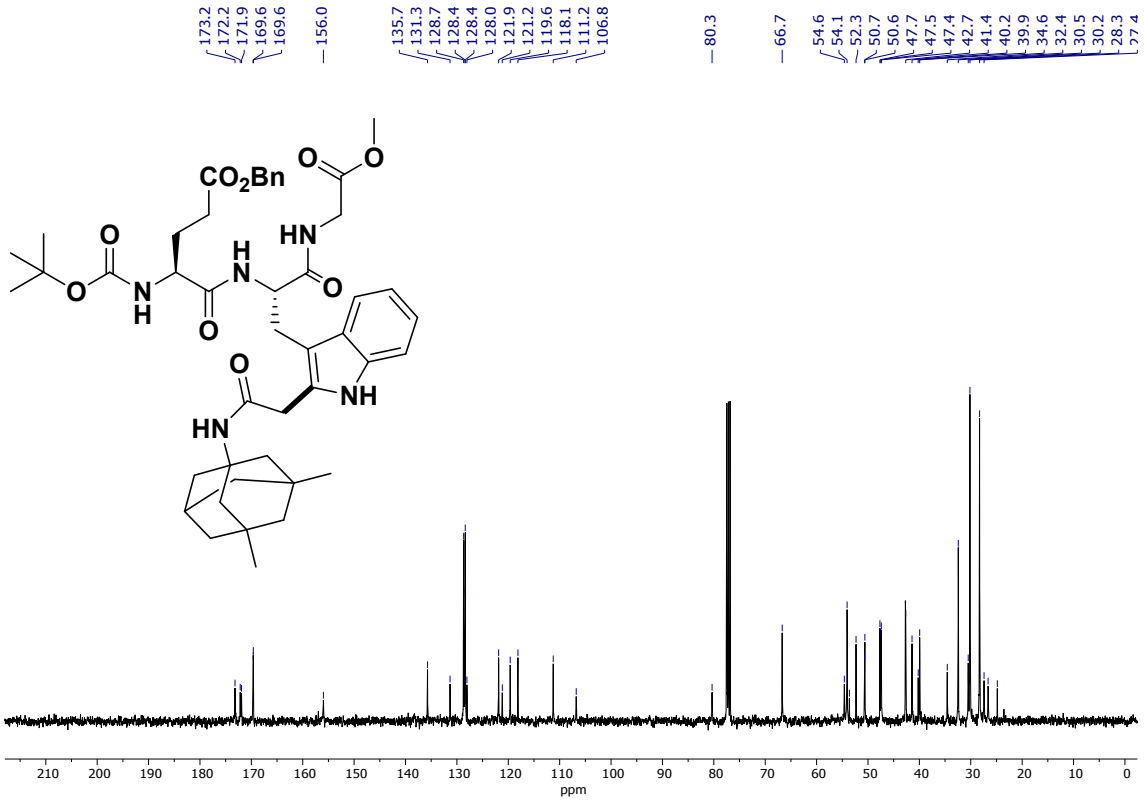


Figure S148. ^{13}C NMR (101 MHz, $CDCl_3$) of **4y**

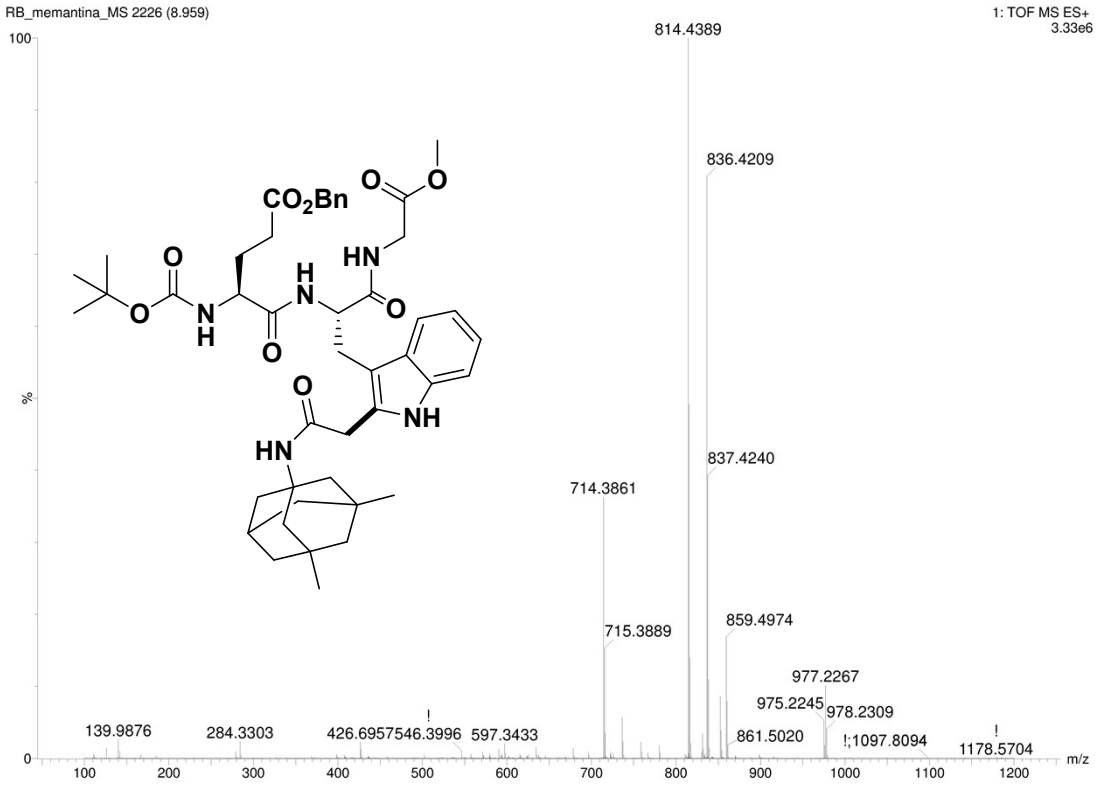


Figure S149. High Resolution Mass Spectra (HRMS) of **4y**

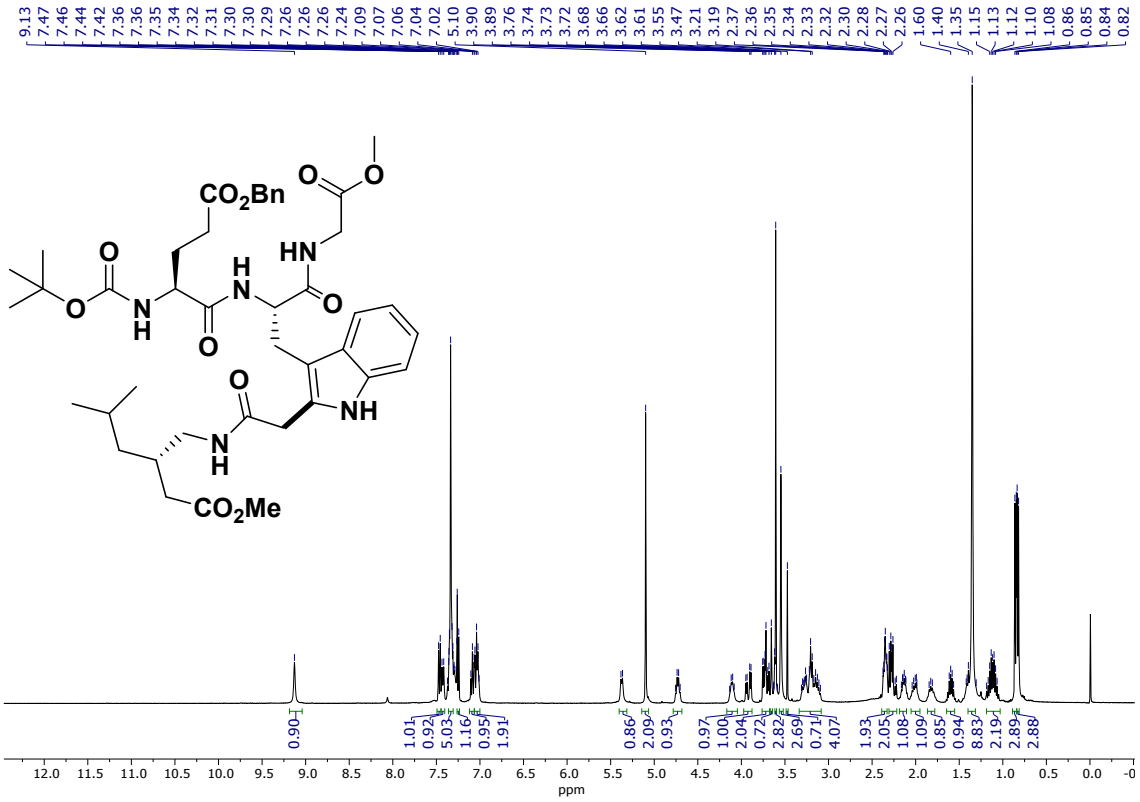


Figure S150. ^{1}H NMR (400 MHz, $CDCl_3$) of **4z**

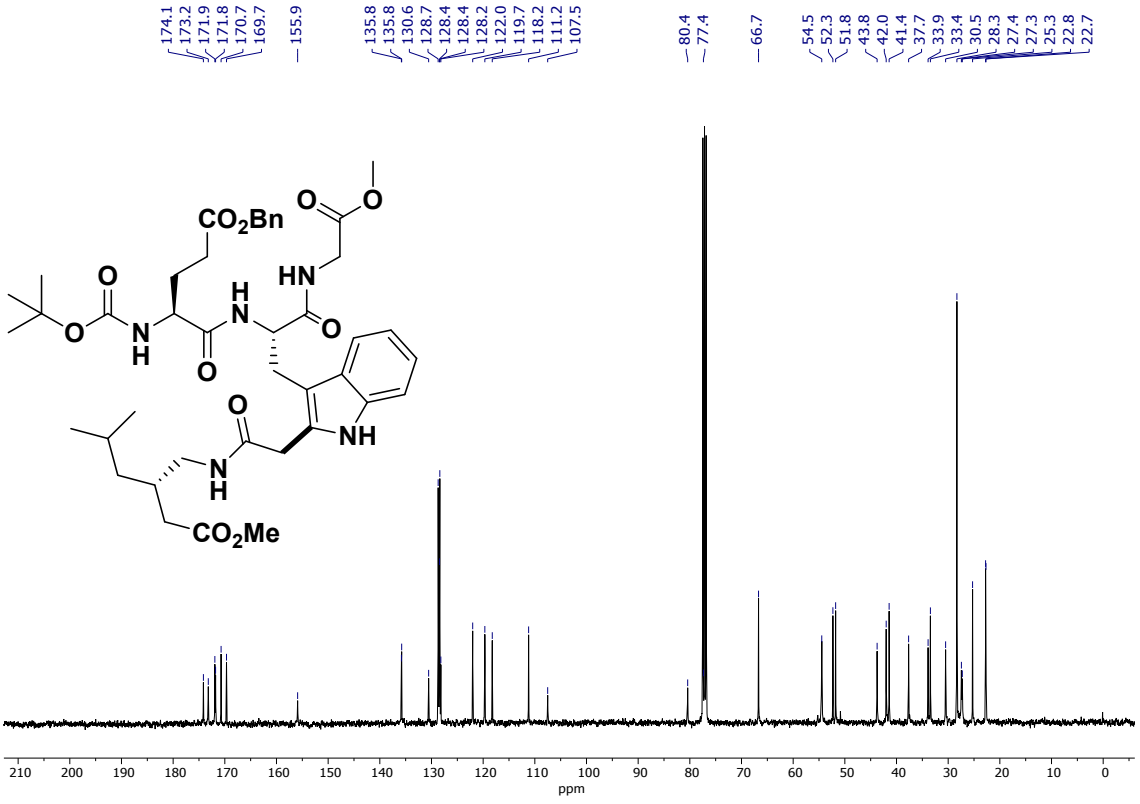


Figure S151. ^{13}C NMR (101 MHz, $CDCl_3$) of **4z**

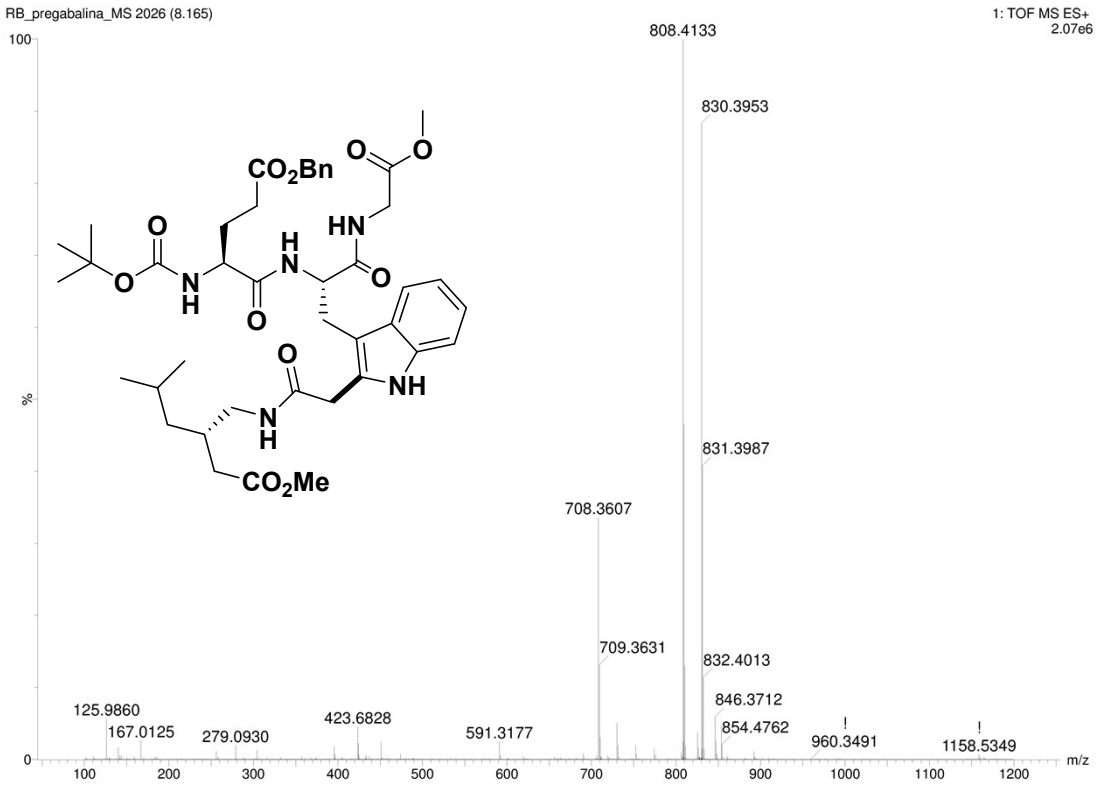
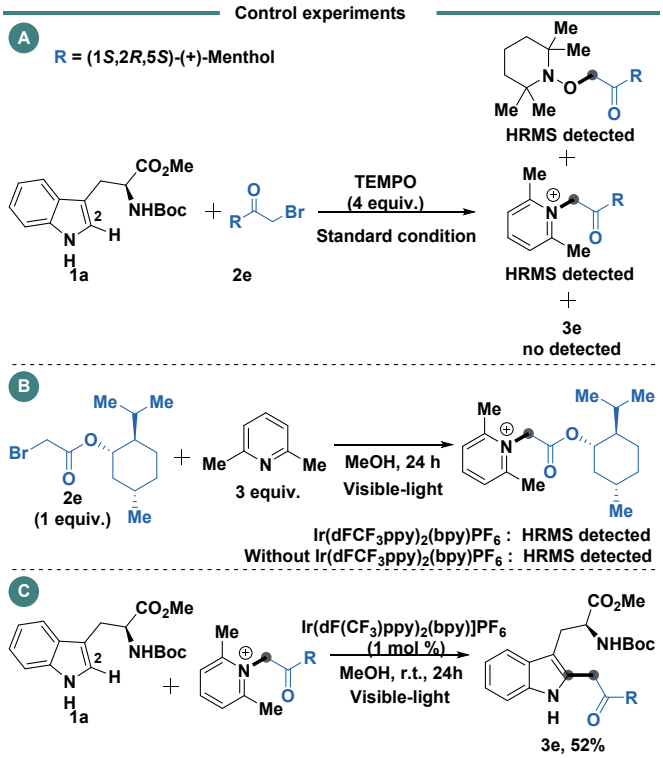


Figure S152. High Resolution Mass Spectra (HRMS) of **4z**

9. Mechanistic studies

A series of control experiments were conducted to better rationalize the sequence of events presented in the reaction mechanism. To confirm a radical species formation, a standard alkylation reaction was attempted in the presence of a radical scavenger. When 4.0 equiv. of TEMPO (2,2,6,6-tetramethylpiperidine-1-oxyl) was added to the reaction mixture, the reaction was completely inhibited. The TEMPO trapped adduct could be detected, therefore showing that the alkyl radical species is presented in the reaction mixture (Scheme 1, A). Another specie identified in this reaction was the lutidine-**2e** salt product, detected when **2e** and 2,6-lutidine reacted with or without iridium catalyst (Scheme 1, B). After the isolation of the lutidine-2e salt and set up of catalytic reaction, product 3e was obtained in 52%. (Scheme 1, C).



Scheme S1. Control experiments.

9.1. Trapping Experiment

The radical-trapping experiment was carried out using TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) as radical scavenger. The starting material **1** (64 mg, 0.2 mmol), **2e** (28 mg, 0.1 mmol), 2,6-lutidine (35 µL, 0.3 mmol), the photocatalyst Ir{dFCF$_3$ppy}$_2$(bpy)PF$_6$ (1 mol %) and TEMPO (4.0 equiv) were dissolved in 0.2 mL of MeOH in a dried Schlenk tube equipped with a stir bar. The Schlenk tube was sealed with PTFE/silicon septum and connected to a vacuum line and the solution was degassed 3 times via a freeze-pump-thaw procedure. The resulting solution was stirred at a distance of ~2 cm under irradiation by a Kessil A360N E-Series Tuna Blue, 90W visible light LED for 24 h.

After the aformentioned reaction time, the product **3e** could not be observed on TLC plate. An aliquot was removed from the extracted crude reaction and a sample was prepared in 1% HCOOH/ MeOH and analyzed by mass spectrometry using an ACQUITY UPC2-MS apparatus via direct infusion.

The MS full scan experiment indicated the presence of the radical scavenger and the starting materials **1** as showed in Figure 138. Additionally, the peak at [M+K$^+$]= 392.2979 would be an evidence of the trapping of the starting material-**2e** by TEMPO. This peak was selected and the further injection in daughter ion scan displayed the ions related to **2e** [M+K$^+$]= 236.1173 and the radical scavenger [M+Na$^+$]= 179.1281 corroborating as evidence of a possible trapped radical generated from the starting material (Figure 139). High-resolution analysis of crude recation confirm the results discussed previously identifying **2e**-TEMPO adduct (Figure 140).

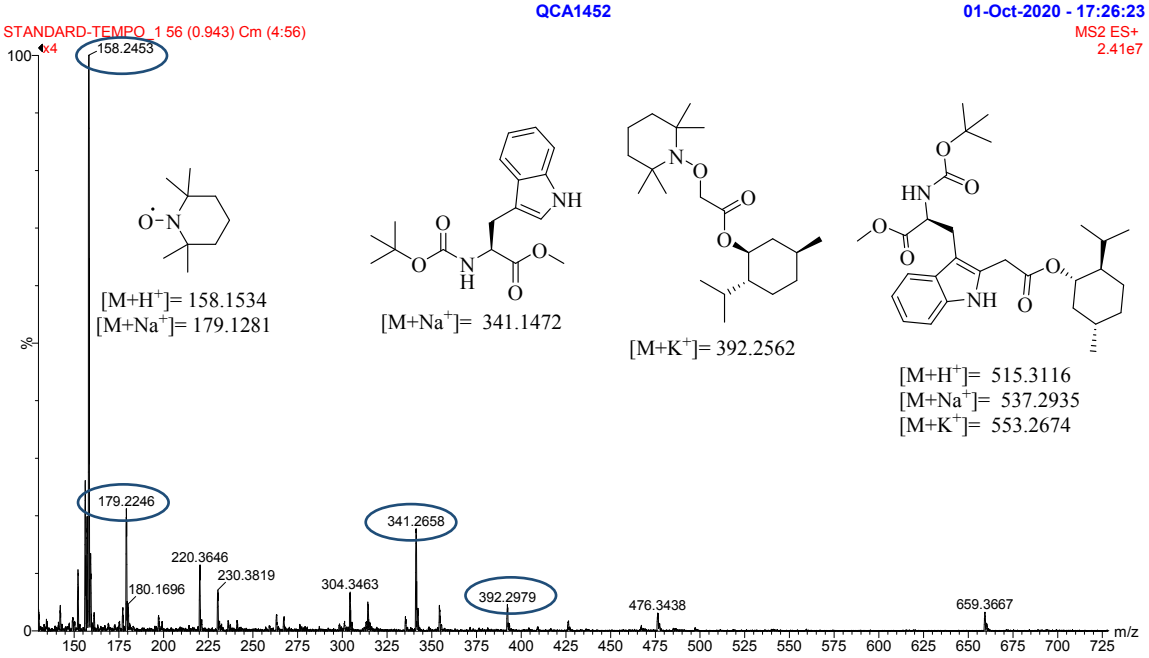


Figure S153. Crude UPC2-MS of standard reaction to obtain product **3e**

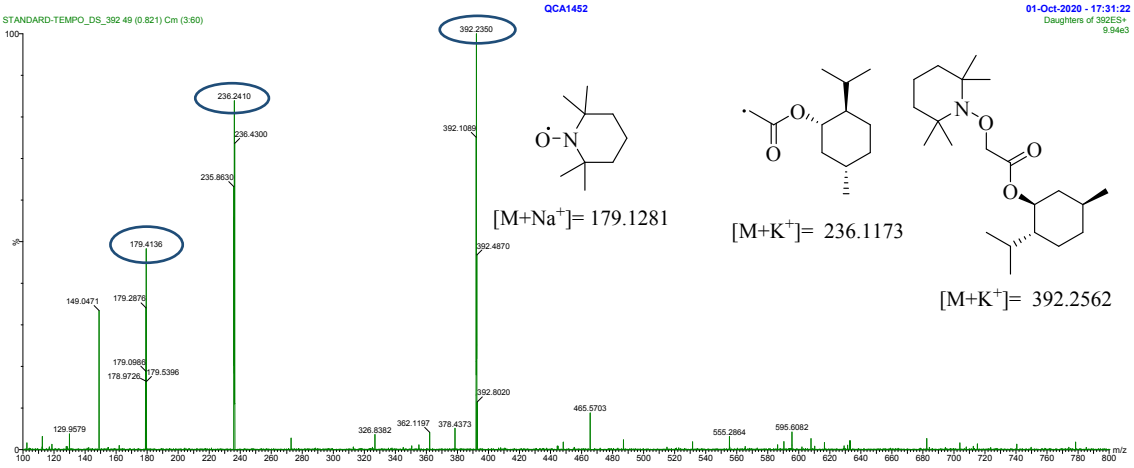


Figure S154. Daughters fragments of adduct-**2e**

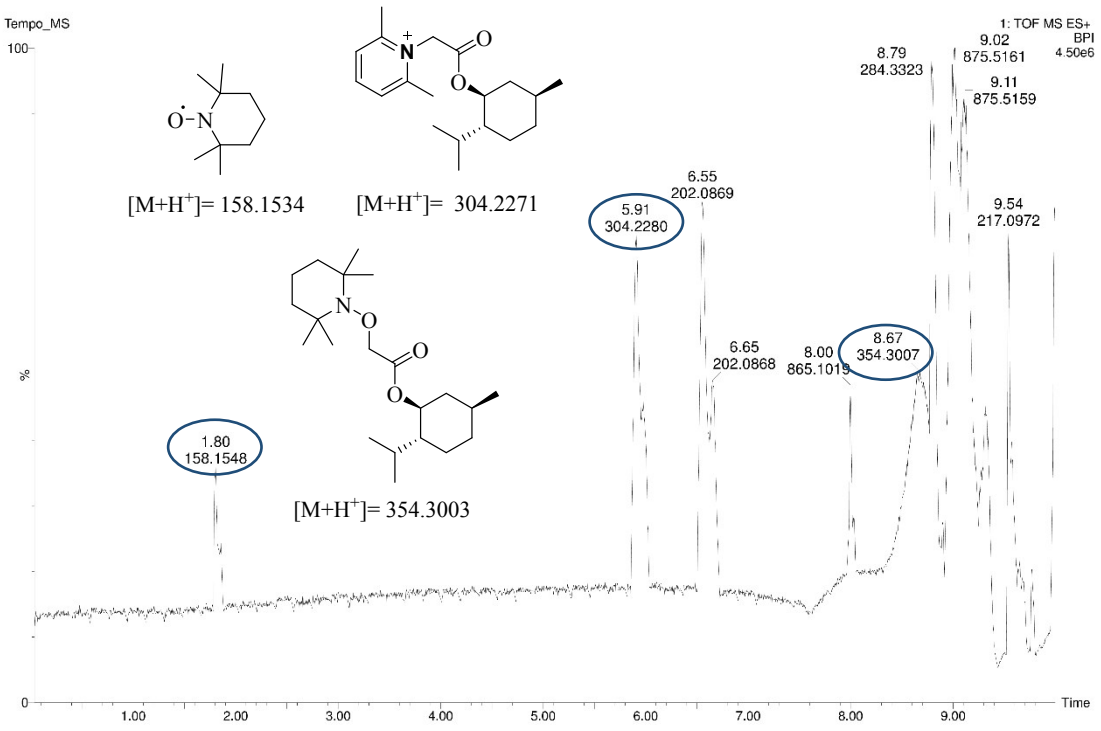


Figure S155. High resolution chromatogram of trapping crude reaction

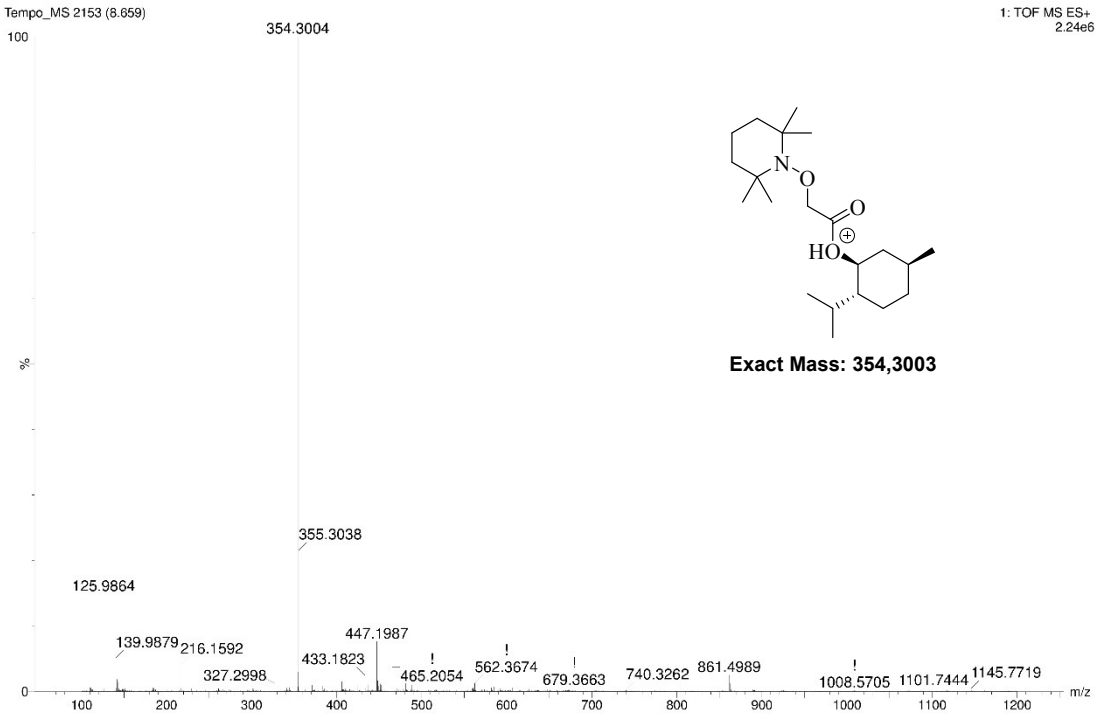


Figure S156. High Resolution Mass Spectra (HRMS) of adduct-**2e**

9.2. Cyclic voltammetry studies

The cell used for cyclic voltammetry measurement consisted of an Ag/AgCl reference electrode, a Pt counter electrode and a CV working electrode. The measurement was conducted on solution of 6 mM of components prepared in 0.1 M tetrabutylammonium tetrafluoroborate ($TBA.BF_4$) solution in CH_3CN. The data was recorded using an EletraSyn 2.0 potentiostat (IKA, Germany) using an initial measurement scan rate of 200 mV/s. The data was plotted with the Excel software.

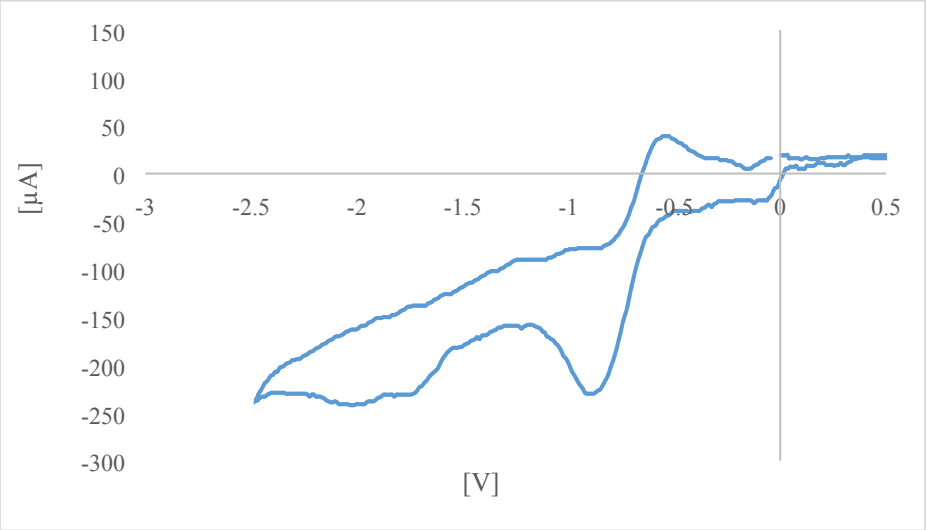


Figure S157. Cyclic voltammetry measurement of control $TBA.BF_4$ solution (0.1 mM)

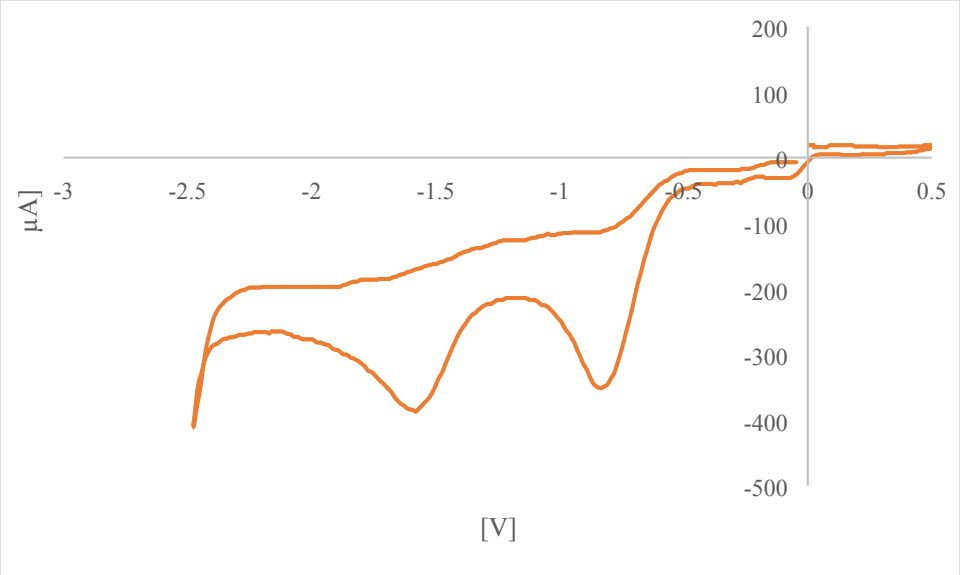


Figure S158. Cyclic voltammetry measurement of compound **2e** in $TBA.BF_4$ solution (0.1 mM)

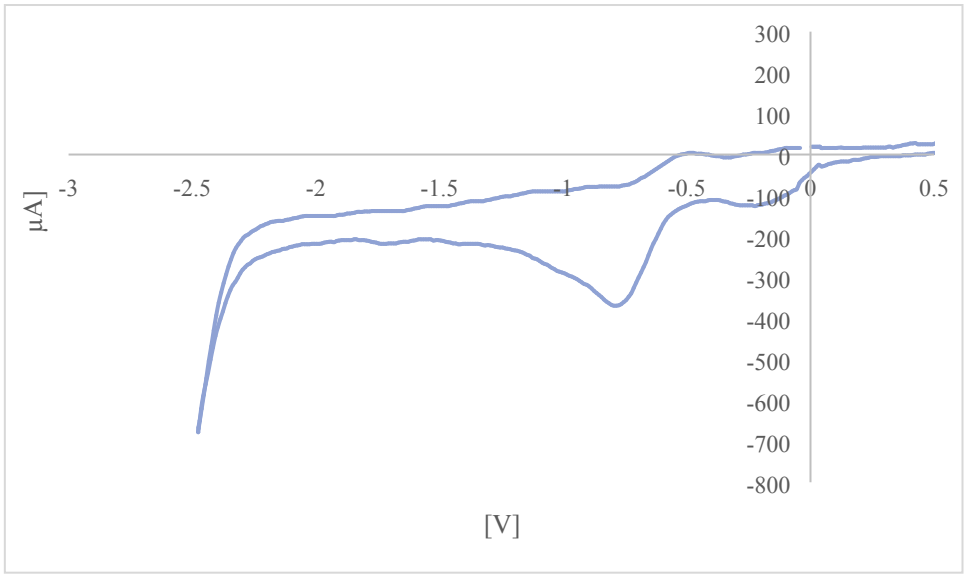


Figure S159. Cyclic voltammetry measurement of lutidine-mentol-salt **3** in TBA.BF_4 solution (0.1 mM)

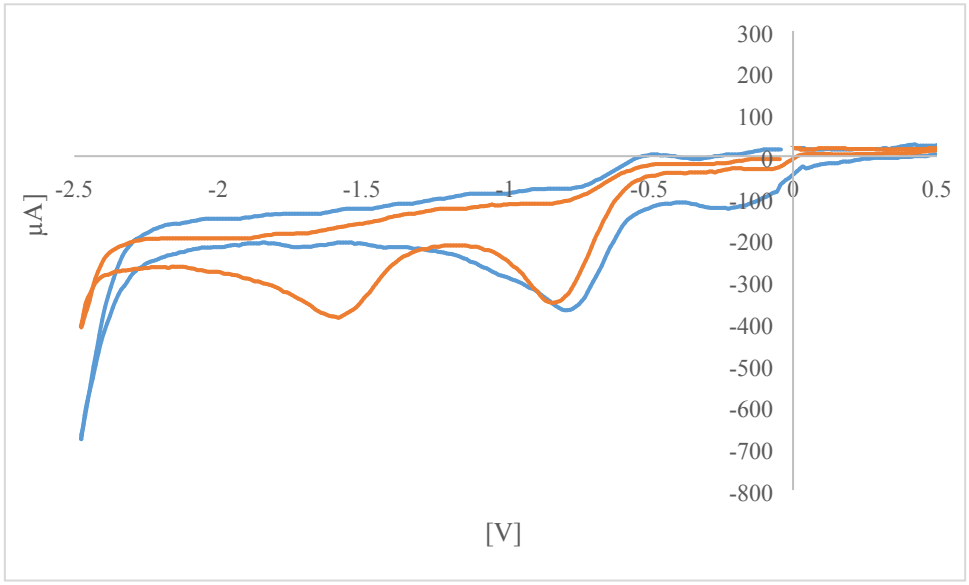
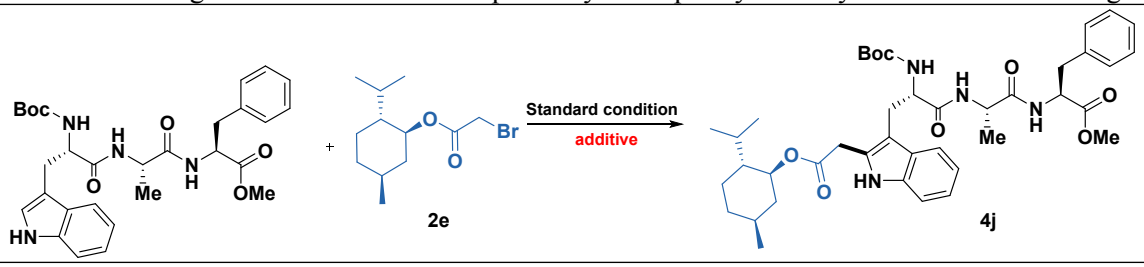


Figure S160. Cyclic voltammetry comparison of **2e** e lutidine-mentol-salt **3** in TBA.BF_4 solution (0.1 mM)

10. Bio-robustness of the iridium-photocatalyzed alkylation of Trp-containing peptide

As depicted in Table 1, the photocatalytic process of the Trp-peptide alkylation was performed in the presence of four distinct amino acids under the optimal reaction condition. Consequently, in the presence of L-lysine and L-methionine a decrease of around 20-30% in the reaction yield were observed, and *L*-histidine shut down completely the reaction. The *L*-glutamic acid showed good compatibility, decreasing less than 10% in the standard reaction yield.

Table 1. Investigation of reaction biocompatibility for Trp-alkylation by bio-additive screening



Entry	Product yield (%)	Additive
1	72	-
2	64	*L*-Glutamic acid (0.1 mmol)
3	53	*L*-Lysine (0.1 mmol)
4	38	*L*-Methionine (0.1 mmol)
5	0	*L*-Histidine (0.1 mmol)

Biocompatibility for Trp-containing tripeptide alkylation. Condition: peptide Boc-Trp-Phe-Ala-OMe (0.2 mmol), 2e (0.1 mmol), 2,6-lutidine (3 equiv.), 1 mol% catalyst in MeOH (0.2 mL) for 24 h under visible-light. Yield was determined by ^{1}H-NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard.

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